

# 2014 Toronto Notes

Comprehensive Medical Reference and Review for MCCQE and USMLE II



Editors-in-Chief: Miliana Vojvodic & Ann Young

# Toronto Notes<sup>2014</sup>

Comprehensive medical reference and review for the  
Medical Council of Canada Qualifying Exam Part 1 and the  
United States Medical Licensing Exam Step 2

30th Edition

Editors-in-Chief:  
Miliana Vojvodic and Ann Young

*Wherever the art of medicine is loved,  
there is also a love of humanity.*

*– Hippocrates*



Toronto Notes for Medical Students, Inc.  
Toronto, Ontario, Canada



## Thirtieth Edition

Copyright © 2014 – Toronto Notes for Medical Students, Inc.  
Toronto, Ontario, Canada.  
Typeset and production by Type & Graphics Inc.  
ISBN 978-1-927363-11-9 (30th ed.)

All rights reserved. Printed in Toronto, Ontario, Canada. Toronto Notes 2014 is provided for the sole use of the purchaser. It is made available on the condition that the information contained herein will not be sold or photocopied. No part of this publication may be used or reproduced in any form or by any means without prior written permission from the publisher. Every effort has been made to obtain permission for all copyrighted material contained herein. Previous editions copyright © 1985 to 2014.

Cover design: Karyn Ho and Catherine Kang  
Illustrations: Biomedical Communications, University of Toronto

### Notice:

**THIS PUBLICATION HAS NOT BEEN AUTHORED, REVIEWED OR OTHERWISE SUPPORTED BY THE MEDICAL COUNCIL OF CANADA NOR DOES IT RECEIVE ENDORSEMENT BY THE MEDICAL COUNCIL AS REVIEW MATERIAL FOR THE MCCQE. THIS PUBLICATION HAS NOT BEEN AUTHORED, REVIEWED OR OTHERWISE SUPPORTED BY THE NATIONAL BOARD OF MEDICAL EXAMINERS U.S.A. NOR DOES IT RECEIVE ENDORSEMENT BY THE NATIONAL BOARD AS REVIEW MATERIAL FOR THE USMLE.**

The editors of this edition have taken every effort to ensure that the information contained herein is accurate and conforms to the standards accepted at the time of publication. However, due to the constantly changing nature of the medical sciences and the possibility of human error, the reader is encouraged to exercise individual clinical judgement and consult with other sources of information that may become available with continuing research. The authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this textbook, atlas, or software and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. In particular, the reader is advised to check the manufacturer's insert of all pharmacologic products before administration.

### FEEDBACK AND ERRATA

We are constantly trying to improve the Toronto Notes and welcome your feedback. If you have found an error in this edition please do not hesitate to contact us. As well, we look forward to receiving any comments regarding any component of the Toronto Notes package and website.

Please send your feedback to: [feedback@torontonotes.ca](mailto:feedback@torontonotes.ca)

Alternatively, send mail to: Toronto Notes for Medical Students  
Editors-in-chief  
c/o The Medical Society  
1 King's College Circle, Room 2171A  
Toronto, Ontario M5S 1A8  
Canada  
email: [chiefeditors@torontonotes.ca](mailto:chiefeditors@torontonotes.ca)  
Tel: 1-416-946-3047 Fax: 1-416-978-8730

Library of Congress Cataloging-in-Publication Data is available upon request

*Dedicated to all  
past and present contributors  
and  
supporters of Toronto Notes  
who have made the production of the 30th Anniversary Edition possible!*



The Toronto Notes is dedicated to helping fund many charitable endeavours and medical student initiatives at the University of Toronto's Faculty of Medicine. Programs that have received Toronto Notes funding include:

**Community Affairs Projects**

- Saturday Program for Inner City High School and Grade 8 students
- St. Felix Mentorship Program for Inner City children
- Parkdale Mentorship Program for Grade 10-12 students
- WoodGreen Community Centre
- Let's Talk Science
- Growing Up Healthy

**Annual Faculty Showcase Events**

- Bruce Tovee Lecture Series
- Daffydil, in support of the Canadian Cancer Society
- Earthtones Benefit Concert
- Convocation and Ceremonies
- Clerkship Luncheon

**Medical School Clubs**

- Books with Wings
- Women in Medicine
- University of Toronto International Health Program
- Complementary and Alternative Medicine
- Peer Support for Students
- History of Medicine Society
- Faculty of Medicine Yearbook

**Scholarships and Bursaries**

- Nishant Fozdar Memorial Award
- Graduating Medical Class Scholarships and Bursaries

**NOTE:**

Many of you have wondered about the *Toronto Notes* logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius' healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

Thomas O'Brien, MD  
Class of 2009  
M.D. Program, University of Toronto

# Preface – From the Editors

Dear Readers,

As Editors-In-Chief of *Toronto Notes* 2014, we are proud to celebrate the 30th Anniversary Edition of the present text.

First produced in 1983 from a set of study notes drafted by medical students at the University of Toronto, *Toronto Notes* has grown to be one of the premier study resources for generations of medical graduates in Canada and abroad. This rich history is rooted in our commitment to publish a student-edited, comprehensive study resource to serve students across clinical rotations and in preparation for the Canadian Medical Licensing Examination (Step 1) and the United States Medical Licensing Examination (Step 2).

Over the past 29 years, our vision has not wavered. We continuously build on the feedback of our readers to enhance the features of the text, handbook and accompanying online resources. The focus of *Toronto Notes* 2014 is to make medical knowledge accessible and retainable by distilling information into high-quality figures, charts and helpful mnemonics. This edition features a new easy-to-view layout across all 29 chapters, with updated text-referencing icons and illustrations. In keeping with rapid advances in medical research, the text also features newly updated best practice guidelines, including recent high-impact trials for clinical practice. The accompanying *Toronto Notes Handbook* also offers new algorithms, flow-charts and new reference cards to serve as a high-yield and portable resource across clinical rotations. This year we are also excited to announce the launch of the first colour edition of the *Toronto Notes eBook* to offer our readers an enhanced mobile learning experience.

*Toronto Notes* 2014 is produced by Toronto Notes for Medical Students Inc., a non-for profit organization supporting various medical student initiatives including community outreach programs, medical school clubs, local charity endeavors, and student bursaries. This year we are especially proud to support the Nishant Fozdar Memorial Award. Nishant was an exceptional medical student, colleague and dear friend in the University of Toronto medical class of 2014. This annual award was established in

his memory, and will be awarded to University of Toronto students who demonstrate Nishant's many qualities, including his dedication to education and community involvement.

Throughout the production of this edition, we have benefited from the gracious help of our student colleagues as well as numerous faculty and administrators at the University of Toronto Faculty of Medicine. Our dedicated team of over 150 students, artists and faculty editors remain the cornerstone of *Toronto Notes* and continue to enhance the text in its' content and clarity each year. We are grateful for our lead editors Andy Tyrell, Vicki Wang, Maria Jogova, Howard Meng, Grace Lam, Hamed Nazzari, Jieun Kim, Daniel Soong, Melini Gupta, Jeffrey Martin and Gautam Goel as well as our 2014 production managers Sheron Perera and Bailey Dyck for their tireless work and dedication to this project. We would also like to acknowledge our partners at Type & Graphics, particularly Enrica Aguilera, for their continued guidance in the production of this text. We also thank our immensely talented cover artists Karyn Ho and Catherine Kang for their innovative vision and immaculate execution of the featured mosaic cover illustration.

Finally we would like to express our deepest gratitude to all previous Editors-In-Chief of *Toronto Notes*. Each editorial team left their unique mark on the text and helped *Toronto Notes* grow into one of the most recognizable student publications in Canada. Much like the pieces in a mosaic, the product of these countless contributions have formed the 30th Anniversary Edition before us today.

On behalf of the 2014 editorial team, we wish you the best in your studies and hope that you will find *Toronto Notes* 2014 to be an asset to your success.

Sincerely,



Miliana Vojvodic, MSc and Ann Young, PhD  
Editors-In-Chief, *Toronto Notes* 2014  
MD Program, University of Toronto



# Acknowledgements

We would like to acknowledge the exceptional work of all previous Toronto Notes (formerly MCCQE Notes) Editors-in-Chief and their editorial teams. The 30th edition of this text was made possible with their contributions.

2013 (29th ed.): Curtis Woodford and Christopher Yao  
2012 (28th ed.): Jesse M. Klostranec and David L. Kolin  
2011 (27th ed.): Yingming Amy Chen and Christopher Tran  
2010 (26th ed.): Simon Baxter and Gordon McSheffrey  
2009 (25th ed.): Sagar Dugani and Danica Lam  
2008 (24th ed.): Rebecca Colman and Ron Somogyi  
2007 (23rd ed.): Marilyn Heng and Joseph Ari Greenwald  
2006 (22nd ed.): Carolyn Jane Shiau and Andrew Jonathan Toren  
2005 (21st ed.): Blair John Normand Leonard and Jonathan Chi-Wai Yeung  
2004 (20th ed.): Andrea Molckovsky and Kashif S. Pirzada  
2003 (19th ed.): Prateek Lala and Andrea Waddell  
2002 (18th ed.): Neety Panu and Sunny Wong  
2001 (17th ed.): Jason Yue and Gagan Ahuja  
2000 (16th ed.): Marcus Law and Brian Rotenberg  
1999 (15th ed.): Sofia Ahmed and Matthew Cheung  
1998 (14th ed.): Marilyn Abraham and M Appleby  
1997 (13th ed.): William Harris and Paul Kurdyak  
1996 (12th ed.): Michael B. Chang and Laura J. Macnow  
1995 (11th ed.): Ann L. Mai and Brian J. Murray  
1994 (10th ed.): Kenneth Pace and Peter Ferguson  
1993 (9th ed.): Joan Cheng and Russell Goldman  
1992 (8th ed.): Gideon Cohen-Nehemia and Shanthi Vasudevan  
All former Chief Editors from 1991 (7th ed.) to 1985 (1st ed.)

# Student Contributors

## Editors-in-Chief

Miliana Vojvodic  
Ann Young

## Production Managers

Bailey Dyck  
Sheron Perera

## Clinical Handbook Editors

Andrew Tyrrell  
Vicki Wang

## Atlas Editors and

**Medical Imaging**  
Hussein Jaffer  
Anish Kapadia

## Online Editor

Nicholas Tassone

## Copy Editors

Michael Beyea  
Danielle Bourque  
Laura Burnes  
Carlo Cifelli  
Caroline Diorio  
Madison Dennis  
Brianna Empringham

Kaitlin Graham  
Cassandra Greenberg  
Sherry Jin  
Olga Malinowska  
Elizabeth Mui  
Ankeeta Tadkase  
Kevin Venus

Farhaad Virjee  
Shintula Wijeyakulasingham  
Wen Yan Xie  
Stacy Yeh  
Andrew Zasowski

## BMC Production Editors

Yi-Min Chun  
Man-San Ma

## Research and Development

Jieun Cha  
Meah Gao  
Howard Meng

## PRIMARY AND OTHER SPECIALTIES

### Associate Editors

Maria Jogova  
Howard Meng

### EBM Editor

Melini Gupta

## MEDICINE

### Associate Editors

Grace Lam  
Hamed Nazzari

### EBM Editor

Gautam Goel

## SURGERY

### Associate Editors

Jieun Kim  
Daniel Soong

### EBM Editor

Jeffrey Martin

## Chapter Editors

### Ethics, Legal and Organizational Medicine

Molly Dingwall  
Jesse Kancir

### Anesthesia

Gavin Hamilton  
Ashwin Sankar

### Clinical Pharmacology

Rick Chen  
Erica Merman  
Monique Moller

### Dermatology

Amanda Carleton  
Thanh-Cat Ho  
Anjali Papneja  
Yuliya Velykoredko

### Emergency Medicine

Neil D. Dattani  
Anandita Gokhale  
Mackenzie Howatt

### Family Medicine

Aaron McGregor  
Joel Moktar  
Amanda Ramdyal  
Amirthini  
Tharmalingam

### Medical Imaging

Ashley Leckie  
Laura Quigley  
Erin Wong

### Pediatrics

Tanvi Agarwal  
Nicole Fischer  
Suparna Sharma  
Wallace Wee

### Population and Community Health

Christine Herrera  
Anisha Prasad  
Anushi Sivarajah

### Psychiatry

Aneta Krakowski  
Emily McDonough  
Tamara Milovic

## Chapter Editors

### Cardiology and Cardiovascular Surgery

Sangiune Laurence  
Lee  
Bryan Ross

### Endocrinology

Yayi Huang  
Angela Liu  
Anna Liu

### Gastroenterology

Ian Brasg  
Ahmad Zaheen

### Geriatric Medicine

Evelyn Cheung  
Christopher Yarnell

### Hematology

Lawson Eng  
Anthony La Delfa

### Infectious Disease

Alice Gray  
Alissa Visram

### Nephrology

Ryan Luther  
Constantin Shuster

### Neurology

Matthew Gladman  
Russell Rasquinha

### Respirology

Amanda Goldberg  
Selena Huang  
Joanna Willms

### Rheumatology

Faranak Esmaeilbeigi  
Richard Norman  
Alex Zhao

## Chapter Editors

### General Surgery

Nicolas Bowers  
Nada Gawad

### Gynecology

Emily Brander  
Jena Hall  
Katherine McLean  
Marina Vainder

### Neurosurgery

Farshad Nassiri  
Johnny Nguyen

### Obstetrics

Rebecca Ronsley  
Jamie Saperia  
Alia Sunderji

### Ophthalmology

Harleen Bedi  
Yao Wang

### Orthopedics

Jonny Elserafi  
Michael Neufeld  
Kajeandra  
Ravichandiran  
David Stockton

### Otolaryngology

Peter Dixon  
Ryan Jude Figueroa

### Plastic Surgery

Stephanie Dreckmann  
Sangita Sequeira

### Urology

Alexandra L. Millman  
Andrew Stewart  
Clare Toguri

## BMC ILLUSTRATORS

Yi-Min Chun  
Nicole Clough  
Jerusha Ellis  
Laura Greenlee  
Karyn Ho

Erin Kezie  
Joshua Lai  
Jean Yi-Chun Lin  
Man-San Ma

Amanda Montanez  
Andrew Q. Tran  
Marissa Webber  
Alice Zheng

# Faculty Contributors, University of Toronto

All contributing professors have been appointed at the University of Toronto.

**David Adam, MD, FRCPC**  
Division of Dermatology  
Department of Medicine  
St. Michael's Hospital

**Anne M. R. Agur, BSc, MSc, PhD**  
Division of Anatomy  
Department of Surgery  
University of Toronto

**Lori Albert, MD, FRCPC**  
Division of Rheumatology  
Department of Medicine  
University Health Network -  
Toronto Western Hospital

**Ruby Alvi, MD, CCFP, MHSc**  
Department of Family  
and Community Medicine  
University of Toronto

**Meyer Balter, MD, FRCPC**  
Division of Respiratory Medicine  
Department of Medicine  
Mount Sinai Hospital

**Nirit Bernhard, MSc, MD, FRCPC**  
Department of Pediatrics  
Hospital for Sick Children

**Andrea Boggild, MSc, MD, FRCPC**  
Tropical Disease Unit and  
Division of Infectious Diseases  
University Health Network -  
Toronto General Hospital

**Esther Bui, MD, FRCPC**  
Division of Neurology and  
Division of Obstetrical Medicine  
Department of Medicine  
Sunnybrook Health Sciences Centre

**Sohail Cheema, MD, FRCPC**  
Department of Pediatrics  
St Michael's Hospital

**Chi-Ming Chow, MDCM, MSc, FRCPC**  
Division of Cardiology  
Department of Medicine  
St. Michael's Hospital

**Tae-Bong Chung, MD, FRCPC**  
Department of Medical Imaging  
Mount Sinai Hospital

**Isabella Devito, MD, FRCPC**  
Department of Anesthesia and  
Pain Management  
University Health Network and  
Mount Sinai Hospital

**Mark Freedman, MD, FRCPC**  
Department of Emergency Medicine  
Sunnybrook Health Sciences Centre

**Sarah Ferguson, MD, FRCSC**  
Division of Gynecologic Oncology  
Department of Obstetrics and Gynaecology  
University Health Network -  
Princess Margaret Hospital

**Barry J. Goldlist, MD, FRCPC**  
Division of Geriatric Medicine  
Department of Medicine  
University Health Network

**Philip C. Hébert, MA, PhD, MD, FCFPC**  
Department of Family and  
Community Medicine  
Joint Centre for Bioethics  
Sunnybrook Health Sciences Centre

**Sender Herschorn, MDCM, FRCSC**  
Division of Urology  
Department of Surgery  
Sunnybrook Health Sciences Centre and  
Women's College Hospital

**Jonathan C. Irish, MD, MSc, FRCSC**  
Department of Otolaryngology -  
Head and Neck Surgery  
University Health Network

**Nasir Jaffer, MD, FRCPC**  
Division of Abdominal Imaging  
Department of Medical Imaging  
Joint Department of Medical Imaging  
University of Toronto

**David Juurlink, BPhM, MD, PhD, FRCPC**  
Division of Clinical Pharmacology  
and Toxicology  
Departments of Medicine and Pediatrics  
Sunnybrook Health Sciences Centre

**Gabor Kandel, MD, FRCPC**  
Division of Gastroenterology, Department of  
Medicine  
St. Michael's Hospital

**Sari L. Kives, MD, FRCSC**  
Department of Obstetrics and Gynaecology  
St. Michael's Hospital and  
The Hospital for Sick Children

**Paul Kuzyk, MASC, MD, FRCSC**  
Division of Orthopedic Surgery  
Department of Surgery  
Mount Sinai Hospital

**Wai-Ching Lam, MD, FRCSC**  
Department of Ophthalmology and  
Vision Science  
University Health Network -  
Toronto Western Hospital

**Chloe Leon, MD, FRCPC**  
Division of Brain and Therapeutics  
Department of Psychiatry  
Centre for Addiction and Mental Health

**Armando Lorenzo, MD, FRCSC**  
Division of Urology  
Department of Surgery  
The Hospital for Sick Children

**Julia Lowe, MBChB, MMedSci, FRCPC**  
Division of Endocrinology and Metabolism  
Department of Medicine  
Sunnybrook Health Sciences Center

**Todd Mainprize, MD, FRCSC**  
Department of Neurosurgery  
Sunnybrook Health Sciences Centre

**Eric Massicotte, MD, MSc, FRCSC**  
Department of Neurosurgery  
University Health Network -  
Toronto Western Hospital

**Michael McDonald, MD, FRCPC**  
Division of Cardiology and  
The Multi-Organ Transplant Program  
Department of Medicine  
University Health Network -  
Toronto General Hospital

**Heather McDonald-Blumer, MD, MSc, FRCPC**  
Division of Rheumatology  
Department of Medicine  
Mount Sinai Hospital

**Filomena Meffe, MD, MSc, FRCSC**  
Department of Obstetrics and Gynaecology  
St. Michael's Hospital

**Yvette Miller-Monthrope, MD, FRCPC**  
Division of Dermatology  
Department of Medicine  
Women's College Hospital

**Azadeh Moaveni, MD, CCFP**  
Department of Family and  
Community Medicine  
University Health Network -  
Toronto Western Hospital

**Eva Mocarski, MD, FRCSC**  
Department of Obstetrics and Gynaecology  
St. Michael's Hospital

**Andrew Morris, MD, SM, FRCPC**  
Division of Infectious Diseases  
Department of Medicine  
Mount Sinai Hospital



# Faculty Contributors, University of Toronto

**Steven Moss, MD, FRCPC**  
Division of Paediatric Emergency Medicine  
Department of Paediatrics  
University of Toronto

**Brian J. Murray, MD, FRCPC, D,ABSM**  
Division of Neurology and Sleep Medicine  
Department of Medicine  
Sunnybrook Health Sciences Centre

**Melinda Musgrave, MD, PhD, FRCSC**  
Division of Plastic and Reconstructive Surgery  
Department of Surgery  
St. Michael's Hospital

**Sharon Naymark, MD, FRCPC**  
Department of Pediatrics  
St. Joseph's Health Centre - Toronto

**Markku T. Nousiainen, MD, MSc, MEd, FRCSC**  
Division of Orthopedic Surgery  
Department of Surgery  
Sunnybrook Health Sciences Centre  
Holland Orthopedic & Arthritic Centre

**Melissa Nutik, MD, CCFP, FCFP**  
Department of Family and  
Community Medicine  
Mount Sinai Hospital

**George Oreopoulos, MD, MSc, FRCSC**  
Division of Vascular Surgery  
Department of Surgery  
University Health Network

**Andrea V. Page, MD, FRCPC**  
Division of Infectious Diseases  
Department of Medicine  
University Health Network

**Susan Poutanen, MD, MPH, FRCPC**  
Department of Microbiology  
University Health Network and  
Mount Sinai Hospital

**Ramesh Prasad, MBBS, MSc, FRCPC**  
Division of Nephrology  
Department of Medicine  
St. Michael's Hospital

**Evan Propst, MD, MSc, FRCSC**  
Division of Head and Neck Surgery  
Department of Otolaryngology  
The Hospital for Sick Children

**Angela Punnett, MD, FRCPC**  
Department of Pediatrics  
The Hospital for Sick Children

**Fran E. Scott, MD, CCFP, FRCPC, MSc**  
Division of Epidemiology  
Dalla Lana School of Public Health

**Phillip Segal, MD, FRCPC**  
Division of Endocrinology and Metabolism  
Department of Medicine  
University Health Network -  
Toronto General Hospital

**Amanda Selk, MD, FRCSC**  
Department of Obstetrics and Gynaecology  
Mount Sinai Hospital

**Marisa Sit, MD, FRCSC**  
Department of Ophthalmology  
and Vision Science  
University Health Network -  
Toronto Western Hospital

**Peter Stotland, MSc, MD, FRCSC**  
Division of General Surgery  
Department of Surgery  
Sunnybrook Health Sciences Centre

**Diana Tamir, MD, FRCPC**  
Department of Anesthesia and  
Pain Management  
University Health Network

**Darrell Tan, MD, PhD, FRCPC**  
Division of Infectious Diseases  
St. Michael's Hospital

**David Tang-Wai, MDCM, FRCPC**  
Division of Neurology and Geriatric Medicine  
Department of Medicine  
University Health Network

**Piero Tartaro, MD, FRCPC**  
Division of Gastroenterology  
Department of Medicine  
University of Toronto

**Fernando Teixeira, MD, FRCPC**  
Department of Emergency Medicine  
St. Michael's Hospital

**Margaret Thompson, MD, FRCPC, FACMT**  
Department of Emergency Medicine  
St. Michael's Hospital and  
The Hospital for Sick Children

**Martina Trinkaus, MD, FRCPC**  
Division of Hematology  
Department of Medicine  
St. Michael's Hospital

**Herbert P. von Schroeder, MD, MSc, FRCSC**  
Divisions of Orthopedic Surgery and  
Plastic Surgery  
Department of Surgery  
University Health Network

**Oshrit Wanono, MD, FRCPC**  
Division of Child and Adolescent Psychiatry  
Department of Psychiatry  
Centre for Addiction and Mental Health

**Richard Ward, MBBS, MRCP, FRCPath**  
Division of Hematology  
Department of Medicine  
University Health Network

**Fay Weisberg, MD, FRCSC**  
Division of Reproductive Endocrinology  
and Infertility  
Department of Obstetrics and Gynaecology  
University of Toronto

**Alice Wei, MD CM, MSc, FRCSC**  
Division of General Surgery  
Department of Surgery  
University Health Network

**Michael Wiley, BSc, MSc, PhD**  
Division of Anatomy  
Department of Surgery  
University of Toronto

**Anna Woo, MD CM, SM, DABIM, FRCPC**  
Division of Cardiology  
Department of Medicine  
University Health Network -  
Toronto General Hospital

**Jensen Yeung, MD, FRCPC**  
Division of Dermatology  
Department of Medicine  
Women's College Hospital

**Elaine Yong, MD, FRCPC**  
Division of Gastroenterology  
Department of Medicine  
Sunnybrook Health Sciences Centre

**Eugene Yu, MD, FRCPC**  
Division of Neuroradiology  
Department of Medical Imaging  
University Health Network

**Alireza Zahirieh, MD, FRCPC**  
Division of Nephrology  
Department of Medicine  
Sunnybrook Health Sciences Centre

# Table of Contents










## Index Abbreviations

1.	Common Unit Conversions	
2.	Commonly Measured Laboratory Values	
3.	Ethical, Legal and Organizational Aspects of Medicine . . . . .	ELOAM
4.	Anesthesia and Perioperative Medicine . . . . .	A
5.	Cardiology and Cardiovascular Surgery . . . . .	C
6.	Clinical Pharmacology . . . . .	CP
7.	Dermatology . . . . .	D
8.	Emergency Medicine . . . . .	ER
9.	Endocrinology . . . . .	E
10.	Family Medicine . . . . .	FM
11.	Gastroenterology . . . . .	G
12.	General Surgery . . . . .	GS
13.	Geriatric Medicine . . . . .	GM
14.	Gynecology . . . . .	GY
15.	Hematology . . . . .	H
16.	Infectious Diseases . . . . .	ID
17.	Medical Imaging . . . . .	MI
18.	Nephrology . . . . .	NP
19.	Neurology . . . . .	N
20.	Neurosurgery . . . . .	NS
21.	Obstetrics . . . . .	OB
22.	Ophthalmology . . . . .	OP
23.	Orthopedics . . . . .	OR
24.	Otolaryngology . . . . .	OT
25.	Pediatrics . . . . .	P
26.	Plastic Surgery . . . . .	PL
27.	Population Health and Epidemiology . . . . .	PH
28.	Psychiatry . . . . .	PS
29.	Respirology . . . . .	R
30.	Rheumatology . . . . .	RH
31.	Urology . . . . .	U
32.	Index	

# How to Use This Book

This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of *Toronto Notes 2014* allows easy identification of important information. These items are indicated by icons interspersed throughout the text:

Icon	Icon Name	Significance
	Key Objectives	This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics.
	Clinical Pearl	This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text.
	Memory Aid	This icon is found in sidebars of the text. It identifies helpful mnemonic devices and other memory aids.
	Clinical Flag	This icon is found in sidebars of the text. It indicates information or findings that require urgent management or specialist referral.
	Cross-Reference	This icon is found in sidebars of the text. It indicates a cross-reference for information that is discussed in a separate chapter.
	Evidence Based Medicine	This icon is found in sidebars of the text. It identifies key research studies for evidence-based clinical decision making related to topics discussed in the accompanying text.
	Colour Photo Atlas	This icon is found next to headings in the text. It indicates topics that correspond with images found in the Colour Photo Atlas available online. ( <a href="http://www.torontonotes.ca">www.torontonotes.ca</a> ).
	Radiology Atlas	This icon is found next to headings in the text. Indicates topics that correspond to images found in the Radiology Atlas available online. ( <a href="http://www.torontonotes.ca">www.torontonotes.ca</a> )
	Online Resources	This icon is found next to headings in the text. It indicates topics that correspond with electronic resources such as Functional Neuroanatomy or ECGs Made Simple, available online. ( <a href="http://www.torontonotes.ca">www.torontonotes.ca</a> )

## Chapter Divisions

To aid in studying and finding relevant material quickly, each chapter is organized in the following general framework:

### Basic Anatomy/Physiology Review

- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

### Common Differential Diagnoses

- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

### Diagnoses

- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

### Common Medications

- a quick reference section for review of medications commonly prescribed

# Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor

To convert from the SI unit to the conventional unit, **divide** by conversion factor

	Conventional Unit	Conversion Factor	SI Unit
ACTH	pg/mL	0.22	pmol/L
Albumin	g/dL	10	g/L
Bilirubin	mg/dL	17.1	μmol/L
Calcium	mg/dL	0.25	mmol/L
Cholesterol	mg/dL	0.0259	mmol/L
Cortisol	μg/dL	27.59	nmol/L
Creatinine	mg/dL	88.4	μmol/L
Creatinine clearance	mL/min	0.0167	mL/s
Ethanol	mg/dL	0.217	mmol/L
Ferritin	ng/mL	2.247	pmol/L
Glucose	mg/dL	0.0555	mmol/L
HbA1c	%	0.01	proportion of 1.0
Hemoglobin	g/dL	10	g/L
HDL cholesterol	mg/dL	0.0259	mmol/L
Iron, total	μg/dL	0.179	μmol/L
Lactate (lactic acid)	mg/dL	0.111	mmol/L
LDL cholesterol	mg/dL	0.0259	mmol/L
Leukocytes	x 10 <sup>3</sup> cells/mm <sup>3</sup>	1	x 10 <sup>9</sup> cells/L
Magnesium	mg/dL	0.411	mmol/L
MCV	μm <sup>3</sup>	1	fL
Platelets	x 10 <sup>3</sup> cells/mm <sup>3</sup>	1	x 10 <sup>9</sup> cells/L
Reticulocytes	% of RBCs	0.01	proportion of 1.0
Salicylate	mg/L	0.00724	mmol/L
Testosterone	ng/dL	0.0347	nmol/L
Thyroxine (T <sub>4</sub> )	ng/dL	12.87	pmol/L
Total Iron Binding Capacity	μg/dL	0.179	μmol/L
Triiodothyronine (T <sub>3</sub> )	pg/dL	0.0154	pmol/L
Triglycerides	mg/dL	0.0113	mmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
Uric acid	mg/dL	59.48	μmol/L

Celsius → Fahrenheit  $F = (C \times 1.8) + 32$

Fahrenheit → Celsius  $C = (F - 32) \times 0.5555$

Kilograms → Pounds 1 kg = 2.2 lbs

Pounds → Ounces 1 lb = 16 oz

Ounces → Grams 1 oz = 28.3 g

Inches → Centimetres 1 in = 2.54 cm

# Commonly Measured Laboratory Values

Test	Conventional Units	SI Units
<b>Arterial Blood Gases</b>		
pH	7.35-7.45	7.35-7.45
PCO <sub>2</sub>	35-45 mmHg	4.7-6.0 kPa
PO <sub>2</sub>	80-105 mmHg	10.6-14 kPa
<b>Serum Electrolytes</b>		
Bicarbonate	22-28 mEq/L	22-28 mmol/L
Calcium	8.4-10.2 mg/dL	2.1-2.5 mmol/L
Chloride	95-106 mEq/L	95-106 mmol/L
Magnesium	1.3-2.1 mEq/L	0.65-1.05 mmol/L
Phosphate	2.7-4.5 mg/dL	0.87-1.45 mmol/L
Potassium	3.5-5.0 mEq/L	3.5-5.0 mmol/L
Sodium	136-145 mEq/L	136-145 mmol/L
<b>Serum Nonelectrolytes</b>		
Albumin	3.5-5.0 g/dL	35-50 g/L
ALP	35-100 U/L	35-100 U/L
ALT	8-20 U/L	8-20 U/L
Amylase	25-125 U/L	25-125 U/L
AST	8-20 U/L	8-20 U/L
Bilirubin (direct)	0-0.3 mg/dL	0-5 µmol/L
Bilirubin (total)	0.1-1.0 mg/dL	2-17 µmol/L
BUN	7-18 mg/dL	1.2-3.0 mmol/L
Cholesterol	<200 mg/dL	<5.2 mmol/L
Creatinine (female)	10-70 U/L	10-70 U/L
Creatinine (male)	25-90 U/L	25-90 U/L
Creatine Kinase – MB fraction	0-12 U/L	0-12 U/L
Ferritin (female)	12-150 ng/mL	12-150 µg/L
Ferritin (male)	15-200 ng/mL	15-200 µg/L
Glucose (fasting)	70-110 mg/dL	3.8-6.1 mmol/L
HbA1c	<6%	<0.06
LDH	100-250 U/L	100-250 U/L
Osmolality	275-300 mOsm/kg	275-300 mOsm/kg
<b>Serum Hormones</b>		
ACTH (0800h)	<60 pg/mL	<13.2 pmol/L
Cortisol (0800h)	5-23 µg/dL	138-635 nmol/L
Prolactin	<20 ng/mL	<20 ng/mL
Testosterone (male, free)	9-30 ng/dL	0.31-1 pmol/L
Thyroxine (T <sub>4</sub> )	5-12 ng/dL	64-155 nmol/L
Triiodothyronine (T <sub>3</sub> )	115-190 ng/dL	1.8-2.9 nmol/L
TSH	0.5-5 µU/mL	0.5-5 µU/mL
<b>Hematologic Values</b>		
ESR (female)	0-20 mm/h	0-20 mm/h
ESR (male)	0-15 mm/h	0-15 mm/h
Hemoglobin (female)	12.3-15.7 g/dL	123-157 g/L
Hemoglobin (male)	13.5-17.5 g/dL	140-174 g/L
Hematocrit (female)	36-46%	36-46%
Hematocrit (male)	41-53%	41-53%
INR	1.0-1.1	1.0-1.1
Leukocytes	4.5-11 x 10 <sup>3</sup> cells/mm <sup>3</sup>	4.5-11 x 10 <sup>9</sup> cells/L
MCV	88-100 µm <sup>3</sup>	88-100 fL
Platelets	150-400 x 10 <sup>3</sup> /mm <sup>3</sup>	150-400 x 10 <sup>9</sup> /L
PTT	25-35 s	25-35 s
Reticulocytes	0.5-1.5% of RBC	20-84 x 10 <sup>9</sup> /L

# Ethical, Legal and Organizational Aspects of Medicine

Molly Dingwall and Jesse Kancir, chapter editors

Maria Jogova, associate editor

Melini Gupta, EBM editor

Dr. Philip C. Hébert, staff editor

<b>Legal Framework</b> . . . . .	<b>2</b>	<b>Organization of Health Care in Canada</b> . . . . .	<b>15</b>
Sources of Law		Legal Foundation	
<b>Ethical Framework</b> . . . . .	<b>2</b>	History	
Principles of Ethics		Key Principles of the <i>Canada Health Act</i>	
Code of Ethics		Health Care Expenditure and Delivery in Canada	
<b>Specific Issues in Private Health</b>		Ethical Considerations in Resource Allocation and Physicians' Role	
<b>Law and Ethics</b> . . . . .	<b>4</b>	Role of the Provincial Licensing Authorities	
Doctor-Patient Relationship		Licensure and Certification	
Consent and Capacity		Role of Professional Associations	
Consent		<b>The US Health Care System</b> . . . . .	<b>19</b>
Capacity		History	
Confidentiality and Reporting Requirements		Health Care Expenditure and Delivery in the US	
Privacy of Medical Records		Access to Health Services	
Physician Competence and Professional Conduct		Health Care Reform	
Truth Telling		<b>References</b> . . . . .	<b>22</b>
Research Ethics			
Physician-Industry Relations			
Physician Responsibilities Regarding Death			
Role of the Coroner			
Palliative and End-of-Life Care			
Reproductive and Sexual Health Law and Ethics			

Further information on these topics can be found in the *Objectives of the Considerations of the Legal, Ethical and Organizational Aspects of the Practice of Medicine (CLEO)* – which can be downloaded free of charge from the Medical Council of Canada website at <http://mcc.ca/wp-content/uploads/CLEO.pdf>

Canadian law applicable to medical practice varies between jurisdictions and changes over time. Criminal law is nationwide, but non-criminal (civil) law varies between provinces. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.

## Acronyms

AE	adverse event	CPSO	College of Physicians and Surgeons of Ontario	PIPEDA	Personal Information Protection and Electronic Documents Act
AMA	American Medical Association	HCCA	Health Care Consent Act	POA	power of attorney
ART	advanced reproductive technologies	LMCC	Licentiate of the Medical Council of Canada	SDM	substitute decision maker
CCB	Consent and Capacity Board	MCC	Medical Council of Canada		
CMA	Canadian Medical Association	OECD	Organization for Economic Co-operation and Development		
CMPA	Canadian Medical Protective Association				



# Legal Framework

## Sources of Law

Source of Law	Definition	Example
<b>Common Law</b>	Legal rules and principles that define private rights and obligations	Tort Law: defines breaches of civil duty owed to someone else Contract Law: define mutually agreed upon rights and obligations that may result in award of damages if breached
<b>Statutes</b>	Laws passed by provincial legislatures and the federal parliament Basis of province/territory specific health care acts Used to establish the provincial/territorial Licensing and Regulatory Authority for health care professionals	In Ontario: <i>Health Care Consent Act</i> , <i>Personal Information Protection Act</i> Criminal Code of Canada which defines breaches of duty owed to society in general
<b>Constitution</b>	Supreme law of Canada All other laws must be consistent with constitution	Canadian Charter of Rights and Freedoms is part of the constitution and guarantees the rights of life, liberty, security of the person, and equality under the law



### Categories of Health Law and Policy

- **Private:** regulates the relationship between "private" actors, such as Doctor and Patient
- **Public:** regulates the actions of "public" actors such as the provincial and federal governments



# Ethical Framework

## Principles of Ethics

- ethics addresses:
  - 1) the principles and values that help define what is morally right and wrong
  - 2) the rights, duties and obligations of individuals and groups
- the practice of medicine assumes there is one code of *professional* ethics for all doctors and that they will be held accountable by that code and its implications

**Table 1. The Four Principles Approach to Medical Ethics**

Principle	Definition	In Practice Do's	In Practice Don'ts
<b>Autonomy</b>	<ul style="list-style-type: none"> <li>• Recognizes an individual's right and ability to decide for themselves according to his/her beliefs and values</li> <li>• Not applicable to newborns, young children, or in situations where informed consent and choice are not possible or may not be appropriate</li> </ul>	<ul style="list-style-type: none"> <li>• Respect and promote an individual patient's values and preferences in decision making to empower him or her</li> <li>• Understand, appreciate, and respect a patient's decision even if it may differ from the recommendation of the physician</li> <li>• Show fidelity to incapable patient's prior capable views if known, and treat them with worth and dignity</li> </ul>	<ul style="list-style-type: none"> <li>• Doctors are not obliged, and indeed ought not, to comply with patients wishes that are illegal or might be considered to be 'conduct unbecoming a doctor' (unprofessional conduct, falling below the standard of care)</li> <li>• A patient's autonomy may be compromised by illness; the principle of autonomy is not a trump card and must be balanced by the rest of the listed principles</li> <li>• Patients are not expected to act in ways considered 'reasonable' or rational by others as long as they do not harm others</li> </ul>



### Autonomy vs. Competence

**Autonomy:** the right that patients have to make decisions according to their beliefs and preferences.

**Competence:** the ability or capacity to make a specific decision for oneself.

**Table 1. The Four Principles Approach to Medical Ethics** (continued)

Principle	Definition	In Practice Do's	In Practice Don'ts
<b>Beneficence</b>	<ul style="list-style-type: none"> <li>The patient-based 'best interests' standard that combines doing good, avoiding harm, taking into account the patient's values, beliefs, and preferences, so far as these are known</li> <li>Autonomy should be integrated with the physician's conception of a patient's medically-defined best interests</li> <li>The aim is to minimize harmful outcomes and maximize beneficial ones</li> <li>Paramount in situations where consent/choice is not possible or may not be appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Try to ensure that a treatment's benefits outweigh its burdens</li> <li>Recommend treatment based on evidence and professional experience to patients and help them weigh the risks and benefits of various options</li> <li>Where a patient's capacity is compromised, physicians have more authority to act purely in the patient's best interests as defined by the therapeutic relationship but they still ought to do so in ways informed by the patient's known wishes and with the involvement, where possible, of the patient's substitute decision-maker</li> </ul>	<ul style="list-style-type: none"> <li>Do not make a decision without a patient's input (direct or indirect)</li> </ul>
<b>Non-Maleficence</b>	<ul style="list-style-type: none"> <li>Obligation to avoid causing harm; <i>primum non nocere</i> ("First, do no harm")</li> <li>A limit condition of the Beneficence principle</li> </ul>	<ul style="list-style-type: none"> <li>Efforts should be made to reduce error and adverse events and ensure patient safety</li> <li>A key guide for all management plans</li> </ul>	<ul style="list-style-type: none"> <li>Do not recommend a treatment because it will have some harm associated with it</li> </ul>
<b>Justice</b>	<ul style="list-style-type: none"> <li>Fair distribution of benefits and harms within a community, regardless of geography or privilege</li> <li>Concept of fairness: Is the patient receiving what he/she deserves – his/her fair share? Is he/she treated the same as equally situated patients? How do one set of treatment decisions impact on others?</li> <li>Respects rules of fair play and basic human rights, such as freedom from persecution and the right to have one's interests considered and respected</li> </ul>	<ul style="list-style-type: none"> <li>Scarce resources are distributed based on the needs of patients and the benefit they would receive from obtaining a specific resource e.g. organs for transplantation are fairly distributed if they go to those who are the most unwell, who are the most likely to survive the longest with the transplant, and who have waited the longest to receive a transplant</li> </ul>	<ul style="list-style-type: none"> <li>Physicians ought to be 'door openers', not 'gate-closers', for their patients</li> </ul>


**The Canadian Adverse Events Study: The Incidence of Adverse Events among Hospital Patients in Canada**
*CMAJ* 2004;170:1678-1686

**Study:** Hospital charts randomly selected and reviewed in four randomly selected Canadian hospitals for the fiscal year 2000.

**Patients:** 4174 patient charts sampled, 3745 eligible charts (>18 yr of age; nonpsychiatric, nonobstetric, minimum 24 h admission).

**Results:** AE rate was 7.5% per 100 hospital admissions (95% CI 5.7-9.3). Highly preventable AEs occurred in 36.9% of patients with AEs (95% CI 32.0-41.8%) and death occurred in 20.8% (95% CI 7.8%-33.8%). An estimated 1521 additional hospital days were associated with AEs. Patients with AEs were significantly older than those without (mean age [and standard deviation] 64.9 [16.7] v. 62.0 [18.4] yr;  $p=0.016$ ). Men and women experienced equal rates of AEs.

**Conclusions:** The overall incidence rate of AEs of 7.5% suggests that, of the almost 2.5 million annual hospital admissions in Canada similar to the type studied, about 185 000 are associated with an AE and close to 70 000 of these are potentially preventable.

**Adverse Event (AE)**

An unintended injury or complication from health care management resulting in disability, death or prolonged hospital stay.



The CMA Code of Ethics is a quasi-legal standard for physicians. If the law sets a minimal moral standard for doctors, the Code ratchets up these standards.

## Code of Ethics

- CMA developed a Code of Ethics that acts as a common ethical framework for Canadian physicians
  - prepared by physicians for physicians and applies to physicians, residents, and medical students
  - based on the fundamental ethical principles of medicine
  - sources include the Hippocratic Oath, developments in human rights, recent bioethical discussion
  - statements are general in nature
  - CMA policy statements address specific ethical issues not mentioned by the code (e.g. abortion, transplantation, and euthanasia)
- the American Medical Association (AMA) has a Code of Medical Ethics
  - articulates the values of medicine as a profession and defines medicine's integrity
  - source of the profession's authority to self-regulate
  - evolving document that changes as new questions arise; AMA policy positions ("AMA Policy") address current health care issues, the health care system, internal organizational structure, decision-making processes, and medical science and technology

# Specific Issues in Private Health Law and Ethics

## Doctor-Patient Relationship

Ethical Basis	Legal Basis
<ul style="list-style-type: none"> <li>A partnership based on the physician providing expert opinion, information, options, and interventions that allows the patient to make informed choices about his/her health care</li> <li>Within this relationship, the doctor and patient share the goals of positive health outcomes, good communication, honesty, flexibility, sensitivity, informed consent, and respect</li> <li>This relationship has the potential to be unequal due to a power difference <ul style="list-style-type: none"> <li>Patients are ill and lack medical expertise</li> <li>Physicians possess specialized medical knowledge and skills</li> <li>Physicians are in a fiduciary relationship with their patients</li> </ul> </li> <li>Due to the nature of the doctor-patient relationship, the physician will: <ul style="list-style-type: none"> <li>Place the best interests of the patient first</li> <li>Establish a relationship of trust with the patient</li> <li>Follow through on undertakings made to the patient in good faith</li> </ul> </li> <li>The physician will accept or refuse patients requesting care: <ul style="list-style-type: none"> <li>Without consideration of race, gender, age, sexual orientation, financial means, religion or nationality</li> <li>Without arbitrary exclusion of any particular group of patients, such as those known to be difficult or afflicted with serious disease</li> <li>Except in emergency situations, in which case care must be rendered</li> </ul> </li> <li>Once having accepted a patient into care, the physician may terminate the relationship provided: <ul style="list-style-type: none"> <li>It is not an emergency</li> <li>After a reasonable period of time (usually a month) for the patient to find alternate care</li> <li>Adequate notice (usually an explanatory letter by registered mail) has been given to the patient</li> <li>There are other options to find 'medically necessary care' (in other words, in smaller communities with fewer options for care, there may need to be some flexibility in cessation of care)</li> </ul> </li> <li>The reason for termination ought to be 'failure of trust'</li> <li>The physician will not exploit the doctor-patient relationship for personal advantage – for sexual, financial, academic or other purposes</li> <li>The physician will disclose limitations to the patient where personal beliefs or inclinations limit the treatment the physician is able to offer</li> <li>The physician will maintain and respect professional boundaries at all times <ul style="list-style-type: none"> <li>Including physical, emotional, and sexual boundaries</li> <li>Regarding treatment of themselves, their families, and friends</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Duties and rights defined partly by: <ul style="list-style-type: none"> <li>Tort law that allows patients to recover damages for wrongful acts committed against them; the most important are: <ol style="list-style-type: none"> <li>Negligence: breach of a legal duty of care (in tort) which results in damage <ul style="list-style-type: none"> <li>Legal finding, not a medical one</li> <li>Physicians may be found negligent when the following four conditions are met: <ol style="list-style-type: none"> <li>The physician owed a duty of care to the patient (the existence of a doctor-patient relationship generally suffices)</li> <li>The duty of care was breached (e.g. by failure to provide the standard of care) <ul style="list-style-type: none"> <li>The standard of care is one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, and specialization</li> </ul> </li> <li>The patient was injured or harmed</li> <li>The harm or injury was caused by the breach of the duty of care</li> </ol> </li> </ul> </li> <li>Errors of judgment are not necessarily negligent</li> <li>Making the wrong diagnosis is not negligent if a reasonable doctor might have made the same mistake in the same circumstances</li> <li>Failure to reconsider the diagnosis if the patient does not respond to treatment may be negligent</li> <li>Physicians can be held liable for the negligent actions of their employees or other individuals they are supervising</li> </ol></li></ul> </li> <li>B. Battery: the application of force to a person's body without their consent <ul style="list-style-type: none"> <li>Contractual rights and obligations that if breached may result in the award of damages</li> <li>Fiduciary duty of physicians to their patients (i.e. to act in their best interest)</li> </ul> </li> </ul>



In situations in which it would be more difficult for a patient to find alternate "medically necessary care", the physician may need to exhibit some flexibility in cessation of care.



"Failure of trust" situations include "double-doctoring" on the part of the patient and patient threats of violence.



### CPSO Policy: Treating Self and Family Members

Physicians will not diagnose or treat themselves or family members except for minor conditions or in emergencies and then only if no other physician is readily available.



### CPSO Policy: Ending the Physician-Patient Relationship

Discontinuing services that are needed is an act of professional misconduct unless done by patient request, alternative services are arranged, or adequate notice has been given.



### Dealing with Controversial and Ethical Issues in Practice

- Discuss in a non-judgmental manner
- Ensure patients have full access to relevant and necessary information
- Identify if certain options lie outside of your moral boundaries and refer to another physician if appropriate
- Consult with appropriate ethics committees or boards
- Protect freedom of moral choice for students or trainees

Source: MCC-CLEO Objectives 1998

## Consent and Capacity



- the autonomous authorization of a medical intervention by a patient
- applies to acceptance and refusal of treatment

### Ethical Principles Underlying Consent and Capacity

- usually the principle of respect for patient autonomy overrides the principle of beneficence
- where a patient cannot make an autonomous decision (i.e. incapable), it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
- there is a duty to discover, if possible, what the patient would have wanted when capable
- central to determining best interests is understanding the patient's values, beliefs, and cultural or religious background
- more recently expressed wishes take priority over remote ones
- patient wishes may be verbal or written
- patients found incapable to make a specific decision should still be involved in that decision as much as possible
- agreement or disagreement with medical advice does not determine findings of capacity/incapacity
- however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed



#### CPSO Policy Consent

Obtaining valid consent before carrying out medical, therapeutic and diagnostic procedures has long been recognized as an elementary step in fulfilling the doctor's obligations to the patient.

## Consent

### Obtaining Legal Consent

- consent of the patient must be obtained before any medical intervention is provided; consent can be:
  - verbal or written, although written is usually preferred
    - ♦ a signed consent form is only evidence of consent – it does not replace the process for obtaining valid consent (see Figure 1)
    - ♦ what matters is what the patient understands and appreciates, not what the signed consent form states
  - implied (e.g. a patient holding out their arm for an immunization) or expressed
- consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm
- *Health Care Consent Act* (of Ontario) covers consent to treatment, admission to a facility, and personal assistance services (e.g. home care)

### Four Basic Requirements of Valid Consent

#### 1. Voluntary

- consent must be given free of coercion or pressure (e.g. from parents or other family members who might exert 'undue influence')
- the physician must not deliberately mislead the patient about the proposed treatment

#### 2. Capable

- the patient must be able to understand and appreciate the nature and effect of the proposed treatment

#### 3. Specific

- the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (i.e. the patient must be informed if students will be involved in providing the treatment)

#### 4. Informed

- sufficient information and time must be provided to allow the patient to make choices in accordance with their wishes. This information should include:
  - ♦ the nature of the treatment or investigation proposed and its expected effects
  - ♦ all significant risks and special or unusual risks
  - ♦ alternative treatments or investigations and their anticipated effects and significant risks
  - ♦ the consequences of declining treatment
  - ♦ risks that are common sense need not be disclosed (i.e. bruising after venipuncture)
  - ♦ answers to any questions the patient may have
- the reasonable person test – the physician must provide all information that would be needed "by a reasonable person in the patient's position" to be able to make a decision
- disclose common adverse events (>1/200 chance of occurrence) and serious risks (e.g. death) even if remote
- it is the physician's responsibility to make reasonable attempts to ensure that the patient understands the information
- physicians should not withhold information about a legitimate therapeutic option based on personal conscience (e.g. not discussing the option of emergency contraception)



#### 4 Basic Elements of Consent

- Voluntary
- Capable
- Specific
- Informed



The Supreme Court of Canada expects physicians to disclose the risks that a "reasonable" person would want to know. In practice, this means disclosing minor risks that are common as well as serious risks that happen infrequently, especially those risks that are particularly relevant to a particular patient (e.g. hearing loss for a musician).

## Exceptions to Consent

### 1. Emergencies

- treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their substitute decision maker (SDM)
- emergency treatment should not violate a prior expressed wish of the patient (e.g. a signed Jehovah's Witness card)
- if patient is incapable, MD must document reasons for incapacity and why situation is emergent
- patients have a right to challenge a finding of incapacity as it removes their decision-making ability
- if a SDM is not available, MD can treat without consent until the SDM is available or the situation is no longer emergent

### 2. Legislation

- Mental Health legislation allows for:
  - ♦ the detention of patients without their consent
  - ♦ psychiatric outpatients may be required to adhere to a care plan in accordance with Community Treatment Orders (see [Psychiatry](#), PS7)
- Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases (see [Population Health and Epidemiology](#), PH19)

### 3. Special Situations

- public health emergencies (e.g. an epidemic or communicable disease treatment)
- warrant for information by police

## Consequences of Failure to Obtain Valid Consent

- treatment without consent is battery (an offense in tort), even if the treatment is life-saving (excluding situations outlined in exceptions section above)
- treatment of a patient on the basis of poorly informed consent may constitute negligence, also an offense in tort
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)



### Major Exceptions to Consent

- Emergencies
- Communicable diseases
- Mental Health legislation



Administration of treatment for an incapable patient in an emergency situation is applicable if the patient is:

- Experiencing extreme suffering
- At risk of sustaining serious bodily harm if treatment is not administered promptly



Patients may also ask to waive the right to choice (e.g. "You know what's best for me, doctor") or delegate their right to choose to someone else (e.g. a family member).



### Consent

- Treatment without consent = battery, including if NO consent or if WRONG procedure
- Treatment with poor or invalid consent = negligence



### CPSO Policy on Capacity

Capacity is an essential component of valid consent, and obtaining valid consent is a policy of the CMA and other professional bodies.

## Capacity

- capacity is the ability to:
  - understand information relevant to a treatment decision
  - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
- capacity is specific for each decision (e.g. a person may be capable to consent to having a chest x-ray, but not for a bronchoscopy)
- capacity can change over time (e.g. temporary incapacity secondary to delirium)
- most Canadian jurisdictions distinguish capacity to make health care decisions from capacity to make financial decisions; a patient may be deemed capable of one, but not the other
- a person is presumed capable unless there is good evidence to the contrary
- capable patients are entitled to make their own decisions
- capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny
- capacity assessments must be conducted by a physician and, if appropriate, in consultation with other health care professionals (e.g. another physician, a mental health nurse)
- clinical capacity assessment may include:
  - specific capacity assessment (i.e. capacity specific to the decision at hand)
    1. effective disclosure of information and evaluation of patient's reason for decision
    2. understanding of:
      - his/her condition
      - the nature of the proposed treatment
      - alternatives to the treatment
      - the consequences of accepting and rejecting the treatment
      - the risks and benefits of the various options (test: can the patient recite back what you have disclosed?)
    3. for the appreciation needed for decision making capacity, a person must:
      - acknowledge the condition that affects him/herself
      - be able to assess how the various options would affect him or her
      - be able to reach a decision and adhere to it, and make a choice, not based primarily upon delusional belief (test: are their beliefs responsive to evidence?)
  - general impressions
  - input from psychiatrists, neurologists, etc.
- employ "Aid to Capacity Evaluation" (see Table 2)

**Table 2. Aid to Capacity Evaluation**

Ability to understand the medical problem
Ability to understand the proposed treatment
Ability to understand the alternatives (if any) to the proposed treatment
Ability to understand the option of refusing treatment or of it being withheld or withdrawn
Ability to appreciate the reasonably foreseeable consequences of accepting the proposed treatment
Ability to appreciate the reasonably foreseeable consequences of refusing the proposed treatment
Ability to make a decision that is not substantially based on delusions or depression

Adapted from Etchells, et al. 1996

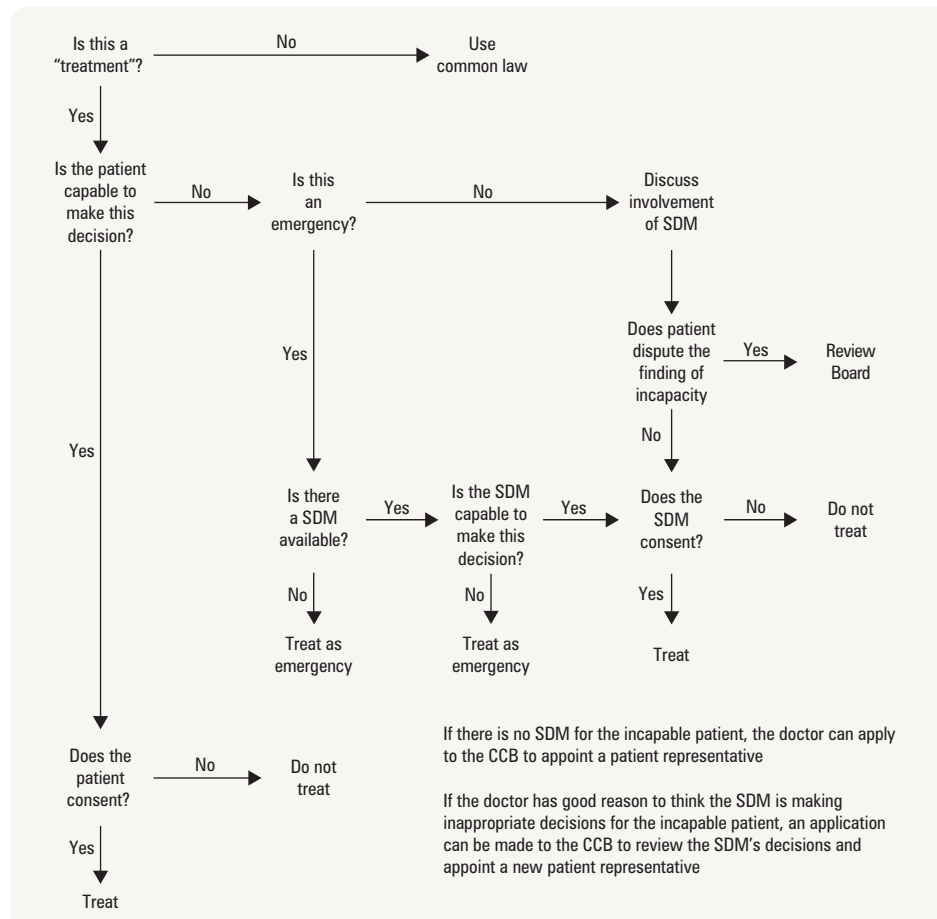
- a decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board), or the courts
- judicial review is open to patients if found incapable

**Treatment of the Incapable Patient in a Non-Emergent Situation**

- obtain informed consent from SDM
- an incapable patient can only be detained against his/her will to receive treatment if he/she meets criteria for certification under the *Mental Health Act*. In such a situation:
  - document assessment in chart
  - notify patient of assessment using appropriate Mental Health Form(s) (Form 42 in Ontario)
  - notify Rights Advisor

**SUBSTITUTE DECISION MAKERS (SDMs)**

- SDM must follow the following principles when giving informed consent:
  - act in accordance with wishes previously expressed by the patient while capable
  - if wishes unknown, act in the patient's best interest, taking the following into account:
    1. values and beliefs held by the patient while capable
    2. whether well-being is likely to improve with vs. without treatment
    3. whether the expected benefit outweighs the risk of harm
    4. whether a less intrusive treatment would be as beneficial as the one proposed
  - the final decision of the SDM may and should be challenged by the MD if the MD believes the SDM is not abiding by the above principles

**Figure 1. Ontario consent flowchart**

SDM = substitute decision maker

Adapted by Hébert P from Sunnybrook Health Sciences Centre Consent Guidelines



Most provinces have legislated hierarchies for SDMs; the hierarchy in Ontario is:

- Legally appointed guardian
- Appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see *Powers of Attorney*, ELOAM8)
- Representative appointed by the Consent and Capacity Board
- Spouse or partner
- Child (age 16 or older) or parent (unless the parent has only a right of access)
- Parent with only a right of access
- Sibling
- Other relative(s)
- Public guardian and trustee



## INSTRUCTIONAL ADVANCE DIRECTIVES

- allow patients to exert control over their care once they are no longer capable
- the patient sets out their decisions about future health care, including who they would allow to make treatment decisions on their behalf and what types of interventions they would want
- takes effect once the patient is incapable with respect to treatment decisions
- in Ontario, a person can appoint a power of attorney for personal care to carry out his/her advance directives
- patients should be encouraged to review these documents with their family and physicians and to reevaluate them often to ensure they are current with their wishes

## POWERS OF ATTORNEY

- all Guardians and Attorneys have fiduciary duties for the dependent person

### Definitions

- **Power of Attorney for Personal Care**
  - a legal document in which one person gives another the authority to make personal care decisions (health care, nutrition, shelter, clothing, hygiene, safety) on their behalf if they become mentally incapable
- **Guardian of the Person**
  - someone who is appointed by the Court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care
- **Continuing Power of Attorney for Property**
  - a legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions
- **Guardian of Property**
  - someone who is appointed by the Public Guardian and Trustee or the Courts to look after an incapable person's property or finances
- **Public Guardian and Trustee**
  - acts as a SDM of last resort on behalf of mentally incapable people who do not have another individual to act on their behalf
- **Pediatric Aspects of Capacity Covered by the HCCA, Ontario**
  - no age of consent; consent depends on patient's decision-making capacity
  - QC has a specific age of consent, but common law and case law deem underage legal minors capable, allowing them to make their own choices; all other provinces and territories do not have an age of consent
  - infants and children are assumed to lack mature decision-making capacity for consent but they should still be involved (i.e. be provided with information appropriate to their comprehension level)
  - adolescents are usually treated as adults
  - preferably, assent should still be obtained from patient, even if not capable of giving consent
  - in the event that the physician believes the SDM is not acting in the child's best interest, an appeal must be made to the local child welfare authorities
  - under normal circumstances, parents have right of access to the child's medical record



There is no age of consent in Ontario.



### Other Types of Capacity Not Covered by the HCCA

- Testamentary (ability to make a will)
- Fitness (ability to stand trial)
- Financial (ability to manage property – Form 21 of the *Mental Health Act*)
- Personal (ability to care for oneself on a daily basis)



### Legal Aspects of Confidentiality

Advice should always be sought from provincial licensing authorities and/or legal counsel when in doubt.



### CMA Code of Ethics

"Disclose your patients' personal health information to third parties only with their consent, or as provided for by law, such as when the maintenance of confidentiality would result in a significant risk of substantial harm to others or, in the case of incompetent patients, to the patients themselves. In such cases take all reasonable steps to inform the patients that the usual requirements for confidentiality will be breached."

## Confidentiality and Reporting Requirements

- a full and open exchange of information between patient and physician is central to a therapeutic relationship
- privacy is a right of patients (which they may forego), while confidentiality is a duty of doctors (which they must respect barring patient consent or the requirements of the law)
- if inappropriately breached by a doctor, he/she can be sanctioned by the hospital, by the court or by his or her regulatory authority
- based on the ethical principal of patient autonomy, patients have the right to:
  - control their own information
  - expect information concerning them will receive proper protection from unauthorized access by others (see *Privacy of Medical Records*, ELOAM9)
- confidentiality may be ethically and legally breached in certain circumstances, e.g. the threat of harm to others
- unlike the solicitor-client privilege, there is no 'physician-patient privilege' by which a physician, even a psychiatrist, can promise the patient absolute confidentiality
- physicians should seek advice from their local health authority or the Canadian Medical Protective Association (CMPA) before disclosing HIV status of a patient to someone else
  - many jurisdictions make mandatory not only the reporting of serious communicable diseases (e.g. HIV), but also the reporting of those who harbour the agent of the communicable disease
  - physicians failing to abide by such regulations could be subject to professional or civil actions
- the legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting cases in the common law

## Statutory Reporting Obligations

- legislation has defined specific instances where public interest overrides the patient right to confidentiality; varies by province, but may include:
  - suspected child abuse or neglect – report to local child welfare authorities (e.g. Children's Aid Society)
  - fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see [Geriatric Medicine](#), GM10)
  - communicable diseases – report to local public health authority (see [Population and Epidemiology](#), PH25)
  - improper conduct of other physicians or health professionals – report to college or regulatory body of the health professional (sexual impropriety by physicians is required reporting in some provinces)
  - vital statistics must be reported; reporting varies by province (in Ontario, births are required to be reported within 30 d to Office of Registrar General or local municipality; death certificates must be completed by a MD then forwarded to municipal authorities)
  - reporting to coroners (see *Physician Responsibilities Regarding Death*, ELOAM13)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

## Duty to Protect/Warn

- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detainment of violent patients for clinical assessment), informing the police, or warning the potential victim(s) if a patient expresses an intent to harm
- first established by a Supreme Court of California decision in 1976; supported by Canadian courts
- obliged by the CMA Code of Ethics and recognized by some provincial/territorial regulatory authorities
- concerns of breaching confidentiality should not prevent the MD from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
- applies in a situation where:
  - there is a clear risk to identifiable person(s);
  - there is a risk of serious bodily harm or death; and
  - the danger is imminent (i.e. more likely to occur than not)

## Disclosure for Legal Proceedings

- disclosure of health records can be compelled by a court order, warrant, or subpoena



### Reasons to Breach Confidentiality

- Child abuse
- Fitness to drive
- Communicable disease
- Coroner report
- Duty to inform/warn



### Ontario's Medical Expert Panel on Duty to Warn

*Ferris et al., 1998*

- There should be a duty to inform when a patient reveals that he/she intends to do serious harm to another person(s) and it is more likely than not that the threat will be carried out
- Where a threat is directed at a person or group and there is a specific plan that is concrete and capable of commission and the method for carrying it out is available to the threatener, the physician should immediately notify the police and, in appropriate circumstances, the potential victim. The report should include the threat, the situation, the physician's opinion and the information upon which it is based



### CMA Code of Ethics

- Protect the health information of your patients
- Provide information reasonable in the circumstances to patients about the reasons for the collection, use and disclosure of their health information
- Be aware of your patient's rights with respect to the collection, use, disclosure and access to their health information; ensure that such information is recorded accurately



### Lock Boxes

The term "lock boxes" applies to situations where the patient has expressly restricted his or her physician from disclosing specific aspects of their health information to others, even those involved in the patient's circle of care.

## Privacy of Medical Records

- privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the *Canadian Charter of Rights and Freedoms*, and the fiduciary duty
- the federal government created the *Personal Information Protection and Electronic Documents Act* (PIPEDA), which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, private labs)
- PIPEDA has been superseded by provincial legislation in many provinces, such as the *Ontario Personal Health Information Protection Act*, which applies more specifically to health information

## Duties of Physicians with Regards to the Privacy of Health Information

- inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
- obtain the patient's expressed consent to disclose information to third parties
  - under Ontario privacy legislation, the patient's expressed consent need not be obtained to share information between health care team members involved in the "circle of care." However, the patient may withdraw consent for this sharing of information and may put parts of the chart in a "lock box"
- provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
- provide secure storage of information and implement measures to limit access to patient records
- ensure proper destruction of information that is no longer necessary

## Physician Competence and Professional Conduct



### CanMEDS Competencies (Ethical/Policy Statement)

- a framework of professional competencies established by the Medical Council of Canada (MCC) as objectives for the Medical Council of Canada Qualifying Exam (MCCQE)
- further information on MCC objectives can be found at [www.mcc.ca](http://www.mcc.ca)

#### 1. Communicator

- display sensitivity to people of all ages, races, cultures, religions, sexual orientations, and genders
- accept or refuse patients without consideration of age, race, culture, religion, sexual orientation, and gender
- understand the variation in values and morals and their impact on approaches to care and decision-making
- elicit patients' beliefs, concerns, and expectations about their illness
- conduct patient-centered interviews, ensure patient comprehension

#### 2. Collaborator

- respect all members of the health care team
- identify the roles and competencies of each member, and delegate tasks appropriately
- consult other physicians and health care professionals effectively and appropriately
- consult with patients and families regarding continuing care plans
- be able to outline co-ordination of services (e.g. Public Health, Home Care, Social Services, Workers' Compensation, Children's Aid Society, etc.)

#### 3. Health Advocate

- identify determinants of health:
  - biological (e.g. genes, impact of lifestyle)
  - physical (e.g. food, shelter, working conditions)
  - social (education, employment, culture, access to care)
- influence public health and health policy to protect, maintain, and promote the health of individuals and the community

#### 4. Manager

- meet regulatory requirements in an office practice (e.g. medical record-keeping, narcotic control, infection control, etc.)
- be prudent in utilization of health care resources, based on anticipated cost-benefit balance
- regulate work schedule such that time is available for continuing education

#### 5. Professional

- maintain standards of excellence in clinical care and ethical conduct
- exhibit appropriate personal and interpersonal behaviour
- enhance clinical competence through lifelong learning
- accept responsibility for personal actions
- do not exploit the physician-patient relationship for personal advantage (e.g. financial, academic)

#### 6. Scholar

- commitment to critical appraisal, constructive skepticism
- participate in the learning of peers and others (e.g. students, health care professionals, patients)

#### 7. Medical Expert

- integration of all CanMEDS competencies to provide patient centred care
- combination of knowledge, clinical skills and judgment, procedural skills and professional behaviour for effective patient care

### Legal Considerations

- the competence and conduct of physicians is legally regulated in certain respects to protect patients and society
- physicians are legally required to maintain a license with the appropriate authority
- physicians must ensure that patients have access to continuous on-call coverage and are never abandoned
- sexual conduct with patients, even when consented to by the patient, is a serious matter that can lead to criminal, civil, and disciplinary action
  - sexual conduct includes intercourse, undue touching, inappropriate reference to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
  - in some situations physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact

### Professional Considerations

#### Elderly Patient

- Identify their resuscitation options (CPR or DNR), if applicable
- Check for documentation of advance directives and POA where applicable
- For further details, see [Geriatric Medicine](#), GM12

#### Pediatric Patient

- Identify the primary decision-maker (parents, guardian, wards-of-state, emancipated)
- Regarding capacity assessment see Pediatric Aspects of Capacity Covered by the HCCA (ELOAM8)
- Be wary of custody issues if applicable

#### Terminally Ill or Palliative Patient

- Consider the SPIKES approach to breaking bad news
- What are their goals of care, i.e. disease vs. symptom management?
- Identify advance directives, POA, or SDM, if applicable (see ELOAM7)
- Check for documentation of resuscitation options (CPR or DNR) and likelihood of success
- For further details, see [Geriatric Medicine](#), GM12

#### Incapable Patient

- If not already present, perform a formal capacity assessment
- Identify if the patient has a SDM or who has their POA
- Check the patient's chart for any Mental Health Forms (e.g. Form 1) or any forms they may have on their person (e.g. Form 42)



### CanMeds Competencies

- Communicator
- Collaborator
- Health Advocate
- Manager
- Professional
- Scholar
- Medical Expert



### CMA Code of Ethics

Report any unprofessional conduct by colleagues to the appropriate authority.

- physicians are permanently prohibited from personal relationships with patients whom they saw for psychotherapy
- in Ontario, physicians must report any colleagues of whom they have information regarding sexual impropriety
- physicians must maintain adequate records for each patient, including:
  - showing that care has been continuous and comprehensive
  - minimal standards for record-keeping include diagnosis, differential diagnosis, appropriate tests and referrals, coherent patient record (full standards available at [www.cpso.on.ca](http://www.cpso.on.ca))
  - keeping records for 10 yr in most jurisdictions
  - although the medical record is the property of the physician or an institution, the patient or the patient's delegate must be allowed full access to information in the medical record upon (usually written) request
- in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain adequate hospital records

## Truth Telling

### Ethical Basis

- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed decisions about health care and their lives

### Legal Basis

- required for valid patient consent (see *Consent and Capacity*, ELOAM5)
  - goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision ("standard of disclosure")
- withholding information can be a breach of fiduciary duty and duty of care
- obtaining consent on the basis of misleading information can be seen as negligent

### Evidence about Truth Telling

- most patients want to know what is wrong with them
- although many patients want to protect family members from bad news, they themselves would want to be informed in the same situation
- truth telling improves compliance and health outcomes
- informed patients are more satisfied with their care
- negative consequences of truth telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability

### Challenges in Truth Telling

#### Medical Error

- medical error may be defined as 'preventable adverse events' caused by the patient's medical care and not the patient's underlying illness. Some errors may be identified before they harm the patient, so not all error is truly 'adverse'
- many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient's family and reported to the appropriate health authorities
- physicians should disclose to patients the occurrence of adverse events or errors caused by medical management, but should not suggest that they resulted from negligence because:
  - a) negligence is a legal determination
  - b) error is not equal to negligence (see *Negligence*, ELOAM4)
- disclosure allows the injured patient to seek appropriate corrective treatment promptly
  - physicians should avoid simple attributions as to cause and sole responsibility of others or oneself
  - physicians should offer apologies or empathic expressions of regret ("I wish things had turned out differently") as these can increase trust and are not admissions of guilt or liability
  - *Apology Acts* across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence

#### Breaking Bad News

- 'bad news' may be any information that reveals conditions or illnesses threatening the patient's sense of well-being
- caution patients in advance of serious tests about possible bad findings
- give warnings of impending bad news (see sidebar for example) and make sure you provide time for the patient
- poorly done disclosure may be as harmful as non-disclosure
- truth-telling may be a process requiring multiple visits
- adequate support should be provided along with the disclosure of difficult news
- SPIKES protocol was developed to facilitate "breaking bad news"



#### CPSO Policy on Truth Telling

Physicians should provide patients with whatever information that will, from the patient's perspective, have a bearing on medical decision-making and communicate that information in a way that is comprehensible to the patient.



#### Examples of warning of impending bad news:

"I have something difficult to tell you...", "This may come as a shock to you, but the tests indicate...", and "There is no easy way for me to tell you this, so I will tell you straight away that you have a serious problem..."



#### Protocol to Break Bad News: SPIKES

- S** Setting the scene and listening skills
- P** Patient's **p**erception of condition and seriousness
- I** Invitation from patient to give information
- K** Knowledge – giving medical facts
- E** Explore emotions and empathize
- S** Strategy and summary

Baile WF and Buckman R 2000

## Arguments Against Truth Telling

- may go against certain cultural norms and expectations
- may lead to patient harm and increased anxiety
- 10-20% of patients prefer not to be informed
- medical uncertainty may result in the disclosure of uncertain or inaccurate information

## Exceptions to Truth Telling

- patients may 'waive' the right to know: patient declines information that would normally be disclosed
- a patient may waive their right to know the truth about their situation when
  - the patient clearly declines to be informed
  - a strong cultural component exists that should be respected and acknowledged
  - the patient may wish others to be informed and make the medical decisions for him/her
- the more weighty the consequences for the patient from non-disclosure, the more carefully one must consider the right to ignorance
- 'Emergencies': an urgent need to treat may legitimately delay full disclosure; the presumption is that most people would want such treatment and the appropriate SDM cannot be found
- 'Therapeutic privilege'
  - withholding information by the clinician in the belief that disclosure of the information would itself lead to severe anxiety, psychological distress or physical harm to the patient
  - clinicians should avoid invoking therapeutic privilege due to its paternalistic overtones and is a defense of non-disclosure that is rarely accepted anymore. It is often not the truth that is unpalatable; it is how it is conveyed that can harm the patient

## Research Ethics



- involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
  - study participants are protected
  - clinical research is conducted to serve the interests of the participants and/or society as a whole
- major ethical dilemmas arise when a physician's obligation to the patient comes into conflict with other obligations and incentives
- any exceptions to disclosure for therapeutic consent do not apply in an experimental situation

**Table 3. Ethical Principles for Research Involving Human Subjects**

- Patient's participation in research should not put him/her at a known or probable disadvantage with respect to medical care (i.e. cannot deny participants in research 'known effective care', for example, unethical to randomize some patients who are depressed to a placebo arm)
- Participant's voluntary and informed choice is usually required
  - Consent may not be required in special circumstances: chart reviews without patient contact; emergency situations for which there is no accepted or helpful standard of care and the proposed intervention is not likely to cause more harm than such patients already face
- Access to the treatment that is considered standard
  - Placebo-controlled trials are generally acceptable where patients still receive the standard of care and are informed about the placebo arm and what that entails
- Must employ a scientifically valid design to answer the research question
  - Scientific rigour ensured via peer review, expert opinion
- Must demonstrate sufficient value to justify the risk posed to participants
- Must be conducted honestly (i.e. carried out as stated in the approved protocol)
- Findings must be reported promptly and accurately without exaggeration, to allow practicing clinicians to draw reasonable conclusions
- Patients must not be enticed into risky research by the lure of money and investigators must not trade the interests of patients for disproportionate recompense by a sponsor; both participants and investigators are due fair recompense for their time and efforts
- Any significant interventional trial ought to have a data safety monitoring board that is independent of the sponsor and can ensure safety of the ongoing trial

Laid out in the Declaration of Helsinki, the Belmont Report, etc.



### Guiding Principles for Research Ethics

- Respect for persons: informed consent
- Beneficence: harm vs. benefit
- Justice: avoid exploitation/unjustified exclusion



### Informed Consent for Research

- Purpose of study
- Sum of funding
- Name and probability of harm and benefits
- Nature of physician's participation including compensation

Proposals for research must be submitted to a research ethics board.



### CMA and CPSO Guidelines for Ethically Appropriate Physician-Industry Relations:

- The primary goal should be the advancement of the health of Canadians
- Relationships should be guided by the *CMA Code of Ethics*
- The physician's primary obligation is to the patient
- Physicians should avoid any self-interest in their prescribing and referral practices
- Physicians should always maintain professional autonomy, independence, and commitment to the scientific method



The *AMA Code of Medical Ethics* has a number of opinions on "Practice Matters" including "Industry representatives in clinical settings," "Financial incentives and the practice of medicine," and "Gifts to physicians from industry," (see <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics.shtml>).

## Physician-Industry Relations

- health care delivery in Canada involves collaboration between physicians and the pharmaceutical and health supply industries in the areas of research, education, and clinical evaluation packages (e.g. product samples)
- physicians have a responsibility to ensure that their participation in such collaborative efforts is in keeping with their duties to their patients and society
- gifts or free products from the pharmaceutical industry are inappropriate
  - sponsorship for travel and fees for conference attendance may be accepted only where the physician is a conference presenter and not just in attendance
  - physicians receiving such sponsorship must disclose this at presentations or in written articles



## Physician Responsibilities Regarding Death

- physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence

## Role of the Coroner

- Coroner's Act* (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
  - due to violence, negligence, misconduct, misadventure, or malpractice
  - during pregnancy or is attributable to pregnancy
  - suddenly and unexpectedly
  - from disease which was not treated by a legally qualified medical practitioner
  - from any cause other than disease
  - under suspicious circumstances
- coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
- in consultation with forensic pathologists and other specialists, the coroner establishes:
  - the identity of the deceased
  - where and when the death occurred
  - the medical cause of death
  - the means of death (i.e. natural, accidental, suicide, homicide or undetermined)
- coroners do not make decisions regarding criminality or legal responsibility



### Notify Coroner if Death Occurs due to:

- Violence, negligence, misconduct
- Pregnancy
- Sudden or unexpected causes
- Disease not treated
- Cause other than disease
- Suspicious circumstances

## Palliative and End-of-Life Care

- focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, loved ones
- appropriate for any patient at any stage of a life-threatening illness
- may occur in a hospital, hospice, in the community or at home
- often an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care

### Euthanasia and Physician-Assisted Suicide

- euthanasia: a deliberate act undertaken by one person with the intention of ending the life of another person to relieve that person's suffering where the act is the cause of death
- physician-assisted suicide: the act of intentionally killing oneself with the assistance of a physician who deliberately provides the knowledge and/or the means
- ethical issues and arguments:
  - right to make autonomous choices about the time and manner of own death
  - belief that there is no ethical difference between the acts of euthanasia/assisted suicide and foregoing life-sustaining treatments
  - belief that these acts benefit terminally ill patients by relieving suffering
  - patient autonomy has limits
  - death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death
- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from euthanasia and assisted suicide as it is seen as allowing the underlying disease to take its 'natural course'
- despite all this, refusals of care by the patient that may lead to death ought to be carefully explored by the physician to rule out any 'reversible factors' (poor palliation, depression, poverty, ill-education, isolation) that may be hindering authentic choice
- law
  - Canada: euthanasia and physician-assisted suicide are punishable offences under the Criminal Code of Canada
  - United States: euthanasia is punishable under general homicide laws; Oregon, Washington, and Montana are the only states to have enacted legislation allowing physicians to actively assist patients who wish to end their lives



### Know the Difference

Palliative care assists patients who are dying, but unlike euthanasia or physician-assisted suicide, it does not aim directly at or intend to end the person's life.



### Euthanasia: Ethically Appropriate Actions

- Respect competent decisions to forgo treatment
- Provide appropriate palliative measures
- Decline requests for euthanasia and assisted suicide
- Try to assess reasons for such requests from patients to see if there are 'reversible factors' (such as depression, pain, loneliness, anxiety) that can be treated

## Reproductive and Sexual Health Law and Ethics

### Maternal-Fetal Relationship

- in general, maternal and fetal interests align
- in some situations a conflict between maternal autonomy and the best interests of the fetus may arise

### Ethical Issues and Arguments

- principle of reproductive freedom: women have the right to make their own reproductive choices
- coercion of a woman to accept efforts to promote fetal well-being is an unacceptable infringement of her personal autonomy

### Legal Issues and Arguments

- law: upholds a woman's right to life, liberty, and security of person and does not recognize fetal rights
  - if a woman is competent and refuses medical advice, her decision must be respected even if the fetus will suffer
  - the fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman
- *Royal Commission on New Reproductive Technologies* recommendations:
  - medical treatment must never be imposed upon a competent pregnant woman against her wishes
  - no law should be used to confine a pregnant woman in the interest of her fetus
  - the conduct of a pregnant woman in relation to her fetus should not be criminalized
  - child welfare should never be used to control a woman's behaviour during pregnancy
  - civil liability should never be imposed upon a woman for harm done to her fetus during pregnancy
- examples of implications
  - a woman is permitted to refuse HIV testing during pregnancy, even if vertical transmission to fetus results
  - a woman is permitted to refuse Caesarean section in labour that is not progressing, despite evidence of fetal distress

### Advanced Reproductive Technologies (ART)

- includes non-coital insemination, hormonal ovarian stimulation, and in vitro fertilization (IVF)
- ethical issues and arguments
  - donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical history)
  - preimplantation genetic testing for diagnosis before pregnancy
  - lack of sufficient data regarding efficacy and complications to provide the full disclosure needed for truly informed consent
  - use of new techniques without patients appreciating their experimental nature
  - embryo status – the Supreme Court of Canada maintains that fetuses are “unique” but not persons under law; this view would likely apply to embryos as well
  - access to ART
    - ♦ private vs. public funding
    - ♦ social factors limiting access to ART (e.g. same-sex couples)
  - against the ‘commercialization’ of reproduction; e.g. payment of gamete donors is currently illegal in Canada
  - however, no regulations as yet means the ART Act is not being enforced; caught in the legal web as to whether such regulations are a provincial or federal responsibility

### Fetal Tissue

- pluripotent stem cells have been derived from human embryonic and fetal tissue
- potential uses of stem cells in research:
  - studying human development and factors that direct cell specialization
  - evaluating drugs for efficacy and safety in human models
  - cell therapy: using stem cells grown *in vitro* to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson's disease)
  - genetic treatment aimed at altering somatic cells (i.e. myocardial or immunological cells) is acceptable and ongoing
  - genetic treatment aimed at altering germ cells is prohibited in Canada and elsewhere
    - ♦ *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Government of Canada, 2010)
    - ♦ see TCPS 2 at: <http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/>
  - embryo research is permitted up to 14 d post-fertilization
  - embryos created for reproductive purposes that are no longer required may be used
  - gamete providers must give free and informed consent for research use
  - no commercial transactions in the creation and use of the embryos is permitted



The fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman.



Once outside the mother's body, the neonate becomes a member of society with all the rights and protections other vulnerable persons receive.

- Non-treatment of a neonate born alive is only acceptable if <22 wk gestational age (GA)
- 23-25 wk GA: treatment should be a consensual decision between physician and parents
- 25 wk GA and more: neonate should receive full treatment unless major anomalies or conditions incompatible with life are present

Source: *Paed Child Health* 2012:443



### Advanced Reproductive Technologies: Ethically Appropriate Actions

- Educate patients and address contributors to infertility (e.g. stress, alcohol, medications, etc.)
- Investigate and treat underlying health problems causing infertility
- Wait at least 1 yr before initiating treatment with ART (exceptions – advanced age or specific indicators of infertility)
- Educate and prepare patients for potential negative outcomes of ART



Surrogate mothers cannot be paid or offered compensation beyond a reimbursement of their expenses.  
Source: Assisted Human Reproduction Act



No one under age 18 can donate sperm or eggs, except for the purpose of creating a child that the donor plans to raise themselves (example: young patients receiving radiation therapy for cancer that may cause infertility).

Source: *Semen Regulations of the Food and Drug Act*



The CMA remains neutral on the issue of embryonic stem cell research.



- creation of embryos solely for research purposes is prohibited
- human cloning is strictly prohibited
- risks of coercion must be minimized:
  - may not pressure fertility treatment team to generate more embryos than necessary
  - only discuss option of using fetal tissue for research after free and informed choice to have a therapeutic abortion has been made
  - physicians responsible for fertility treatment may not be part of a stem cell research team

### Induced Abortion

- CMA definition of induced abortion: the active termination of a pregnancy before fetal viability
  - fetal viability: fetus >500 g, or >20 wk gestational age
- CMA policy on induced abortion:
  - induced abortion should not be used as an alternative to contraception
  - counselling on contraception must be readily available
  - full and immediate counselling services must be provided in the event of unwanted pregnancy
  - there should be no delay in the provision of abortion services
  - no patient should be compelled to have a pregnancy terminated
  - physicians should not be compelled to participate in abortion – if morally opposed, the physician should inform the patient so she may consult another physician
  - no discrimination should be directed towards either physicians who do not perform or assist at induced abortions or physicians who do
  - induced abortion should be uniformly available to all women in Canada and health care insurance should cover all the costs (N.B. the upper limit of gestational age for which coverage is provided varies between provinces)
  - elective termination of pregnancy after fetal viability may be indicated under exceptional circumstances
- ethical and legal issues and arguments:
  - according to common law, the rights of a fetus are not equal to those of a human being
  - no law currently regulates abortion in Canada – it is a woman's medical decision to be made in consultation with whom she wishes; no mandatory role for spouse/family
  - 2nd and even 3rd trimester abortions are not illegal in Canada, but are usually only carried out when there are serious risks to the woman's health or if the fetus has died in utero or has major malformations (e.g. anencephaly)

### Prenatal/Antenatal Genetic Testing

- uses:
  - confirm a clinical diagnosis
  - detect genetic predisposition to a disease
    - ♦ allows preventative steps to be taken and helps patient prepare for the future
  - give parents the option to terminate a pregnancy or begin early treatment
- ethical dilemmas arise because of the nature of genetic information:
  - it has individual and familial implications
  - it pertains to future disease
  - it often identifies disorders for which there are no effective treatments or preventive steps
  - also can be used to identify the sex of the fetus leading to termination of pregnancy if the fetus is of the unwanted sex; this is considered inappropriate by some but is entirely legal as a woman can request an abortion for any reason
- ethical issues and arguments:
  - obtaining informed consent is difficult due to the complexity of genetic information
  - doctor's duty to maintain confidentiality vs. duty to warn family members
  - risk of social discrimination (e.g. insurance) and psychological harm
- law:
  - no current specific legislation exists
  - testing requires informed consent
  - no standard of care exists for clinical genetics but physicians are legally obligated to inform patients that prenatal testing exists and is available
  - breach of confidentiality – duty to warn family members
    - ♦ only acceptable if can likely prevent serious harm, such as if treatment or prevention is available (e.g. familial adenomatous polyposis)



#### Genetic Testing: Ethically Appropriate Actions

- Thorough discussion and realistic planning with patient before testing is done
- Genetic counselling for delivery of complex information, supportive discussion

## Organization of Health Care in Canada

- one federal, three territorial, and ten provincial systems
- federal system provides care to Aboriginal groups, the RCMP, and the armed forces
- financed by both the public (70%) and private (30%) sectors
- each provincial plan must cover all medically necessary health services delivered in hospitals and by physicians; may choose to cover services such as home care and prescription drugs
- non-insured health services and fees are either covered by private insurance or by the individual
- workers' compensation funds cover treatment for work-related injuries and diseases

## Legal Foundation

The legal foundation of the Canadian health system is based on two constitutional documents:

1. *Constitution Act* (1867): deals primarily with the jurisdictional power between federal and provincial governments
2. *The Canadian Charter of Rights and Freedoms* (1982): does not guarantee a right to health care but, given government's decision to finance health care, they are constitutionally obliged to do so consistently with the rights and freedoms outlined in the Charter (including the right to equality, physician's mobility rights, etc.)

And two statutes:

1. *Canada Health Act* (1984): outlines the national terms and conditions that provincial health systems must meet in order to receive federal transfer payments
2. *Canada Health and Social Transfer Act* (1996): federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces' discretion

## History

- 1867 *British North America Act* (now *Constitution Act*) establishes Canada as a confederacy
- government has minimal role in health care at this time
  - "establishment, maintenance, and management of hospitals" under provincial jurisdiction
- 1947 Saskatchewan introduces universal hospital insurance
- based on taxes and premiums
  - other provinces follow
- 1957 Federal government passes *Hospital Insurance and Diagnostic Services Act*
- provinces with universal hospital insurance receives federal funds
  - federal government pays for approximately 50% of insured services
- 1962 Saskatchewan implements universal medical care insurance
- physician services included
- 1965 *Royal Commission on Health Services (Hall Commission)* recommends federal leadership and financial support with provincial government operation
- 1966 *Medical Care Act* passed by federal government
- federal government contribution maintained at 50% on average, with poorer provinces receiving more funds
  - medical insurance must be comprehensive, portable, universal, and publicly administered
- 1977 *Established Programs Financing Act* passed by federal government
- federal government gives "tax points" to provinces by reducing federal taxes and allowing provinces to collect more
  - funding no longer tied to direct services → federal influence wanes
  - provinces bear greater costs and impose restrictions on physicians
  - physicians respond with "extra-billing"; patients pay a supplementary fee
- 1984 *Canada Health Act* passed by federal government
- replaced *Medical Care Act* and *Hospital Insurance and Diagnostic Services Act*
  - extra-billing banned by new fifth criterion: Accessibility
- 1996 *Canada Health and Social Transfer Act* passed by federal government
- federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces' discretion
- 1999 *Social Union Framework Agreement* signed by the Prime Minister and all Premiers and territorial leaders except Quebec
- federal and provincial/territorial governments vow to concentrate their efforts to modernize Canadian social policy
- 2001 *Kirby and Romanow Commissions* appointed
- Kirby Commission* (final report, October 2002)
- one-member committee of the Senate: examined history of health care system in Canada, pressures and constraints of current health care system, role of federal government, and health care systems in foreign jurisdictions
- Romanow Commission* (final report, November 2002)
- one-member royal commission (former Saskatchewan Premier Roy Romanow) appointed by the Prime Minister to inquire into and undertake dialogue with Canadians on the future of Canada's public health care system

- 2003 *First Ministers' Accord on Health Care Renewal* signed
- First Ministers agreed on an action plan to improve access to quality care for all Canadians and to prepare an annual public report on primary and home care
  - First Health Council (composed of government and expert/public representatives) appointed to improve accountability in the health care system
- 2004 *First Ministers' Meeting on the Future of Health Care* produces a 10-yr plan
- priorities include reductions in waiting times, development of a national pharmacare plan, and primary care reform
- 2005 *Chaoulli v. Quebec*, Supreme Court of Canada Decision
- ruled that Quebec's banning of private insurance would be unconstitutional under the Quebec Charter of Rights, given that patients do not have access to those services under the public system in a timely way
  - Quebec government was given one year to respond
- 2011 First progress report by the Health Council reviews progress towards 2004 First Ministers' 10 yr plan
- significant reductions in wait times for specific areas (such as cancer, joint replacement and sight restoration) while these reductions may have inadvertently caused increases in wait times of other services
  - despite large investments into electronic medical records (EMRs), Canada continues to have very low uptake, ranking last in the Commonwealth Fund International Health Policy survey, with use of only 37% use by primary care physicians
  - little progress in creating a national strategy for equitable access to pharmaceuticals; however, there has been some success in increasing pharmacists' scope of practice, reducing generic drugs costs and implementing drug info systems
- Federal Government announces that it will not renew 2004 *First Ministers' Accord on Health Care Renewal*
- increases in funding to provinces at 6% per annum until the 2016-2017 fiscal year, from then onwards, increases tied to nominal GDP at a minimum of 3% per annum
- 2012 Second progress report by the Health Council reviews progress towards 2004 First Ministers' 10 yr plan
- funding is sufficient; however, more innovation is needed including incentivizing through models of remuneration
  - 46 recommendations were made to address the lack of progress in prevention, access to primary-care physicians, long-term, respite and palliative care services, wait-time benchmarks, accountability, IT, Aboriginal health and more
- 2013 Federal Government announces that it will stop funding the Health Council of Canada in 2014
- the council (born in 2004) will close in 2014 leaving no other independent national body to assess the performance of the Canadian health care system
- 2014 Expiry of current *10 Year Health Care Funding Agreement* between Federal and Provincial governments

## Key Principles of the *Canada Health Act*

1. Public Administration
  - provincial health insurance programs must be administered by public authorities
2. Comprehensiveness
  - provincial health insurance programs must cover all necessary diagnostic, physician, and hospital services
3. Universality
  - all eligible residents must be entitled to health care services
4. Portability
  - emergency health services must be available to Canadians who are outside their home province, paid for by the home province
5. Accessibility
  - user fees, charges, or other obstructions to insured health care services are not permitted



The federal government can reduce its contributions to provinces that violate the key principles of the *Canada Health Act*.



### Principles of Canada Health Act

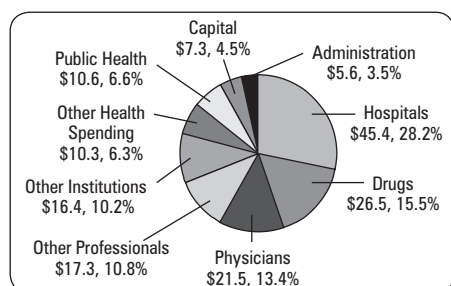
- Public Administration
- Comprehensiveness
- Universality
- Portability
- Accessibility

## Health Care Expenditure and Delivery in Canada

- projected total health care expenditure in 2009 was \$182.1 billion, 11.9% of the GDP, approx. \$4,363 USD per capita (*Canadian Institute of Health Information*)
- 2009 Canadian health care expenditure as a percentage of GDP ranked 6 out of 29 for Organization for Economic Cooperation and Development (OECD) member nations (*Canadian Institute of Health Information*)
- 70.9% of health care spending came from public sector sources in 2009 as compared to 47.7% in the US
- in 2006 there were 2.1 physicians per 1000 population, ranking 26th out of OECD member countries

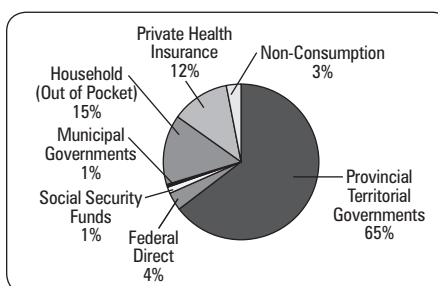
### Delivery of Health Care

- hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities
- this differs from other countries, such as the US (a mix of public and private funding, as well as private-for-profit and private not-for-profit delivery) and the UK (primarily public funding and delivery)



**Figure 2. Health expenditure in Canada by use of funds (billions of dollars), 2009**

Source: Canadian Institute for Health Information. National Health Expenditure Trends. 1975 to 2011



**Figure 3. Canadian health care dollars by source of funds, 2007**

Source: Canadian Institute for Health Information. National Health Expenditure Trends. 1975 to 2009



#### Payments for Care at Private For-Profit and Private Not-for-Profit Hospitals:

##### A Systematic Review and Meta-analysis

CMAJ 2004;170:1817-1824

Meta-analysis of 8 US observational studies involving more than 350 000 patients. Concluded that care provided by private for-profit hospitals was more expensive (Relative payments for care = 1.19; 95% CI = 1.07-1.33; p = 0.001). If half of Canadian hospitals were converted to private for-profit institutions, an extra \$3.6 billion would be paid annually.

## Ethical Considerations in Resource Allocation and Physicians' Role

- the distribution of goods and services to programs and people
- physicians have the duty to inform patients about therapeutic options even if they are not available
- consider justice: physicians must make health care resources available to patients in a manner which is fair and equitable, without bias or discrimination
  - need and benefit are morally relevant criteria for resource allocation
  - gender, sexual orientation, religion, level of education or age alone are morally irrelevant criteria
- ethical dilemmas that arise when deciding how best to allocate resources
  - fair chances versus best outcome: favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
  - priorities problem: how much priority should the sickest patients receive?
  - aggregation problem: modest benefits to many vs. significant benefits to few
  - democracy problem: when to rely on a fair democratic process to arrive at a decision
- guidelines for appropriately allocating resources
  - the physician's primary obligation is to protect and promote the welfare and best interests of his or her patients
  - choose interventions known to be beneficial on the basis of evidence of effectiveness
  - seek the tests or treatments that will accomplish the diagnostic or therapeutic goal for the least cost
  - advocate for one's patients but avoid manipulating the system to gain unfair advantage for them
  - resolve conflicting claims for scarce resources justly, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures
  - inform patients of the impact of cost constraints on care, but in a sensitive way
  - seek resolution of unacceptable shortages at the level of hospital management or government



#### CPSO Policy on Resource Allocation

Physicians should "recognize [their] responsibility to promote fair access to health care resources" and should "use health care resources prudently."

## Role of the Provincial Licensing Authorities

- the medical profession in Canada self-regulates under the authority of provincial legislation;
- physicians in each province are self-regulated by a licensing authority (e.g. College of Physicians and Surgeons of Ontario, the CPSO); membership is mandatory to practice in that province
- self-regulation is based on the premise that the licensing authority must act first and foremost in the interest of the public
- licensing authority functions include:
  - provincial licensing authorities provide non-transferable licensure to physicians
  - issuing non-transferable licenses allow doctors to practice only in that province
  - maintaining ethical, legal, and competency standards and developing policies to guide doctors
  - investigating complaints against doctors
  - disciplining doctors guilty of professional misconduct or incompetence
  - at times of license investiture and renewal, physicians must disclose if they have a condition (such as HIV positivity or drug addiction or other illness that may impact their ability to practice safely)
- in an evolving area of responsibility, physicians may be required to report colleagues who may be a hazard to patients (e.g. the inebriated colleague)

## Licensure and Certification

- the Medical Council of Canada (MCC) certifies physicians
  - certification is known as the Licentiate of the MCC (LMCC)
  - LMCC is acquired by passing the MCC Qualifying Examination Parts I and II
- the Royal College of Physicians and Surgeons of Canada (RCPSC) certifies specialists who complete an accredited residency program and pass the appropriate exam
  - voluntary membership of RCPSC is designated FRCPC or FRCSC (Fellow of the Royal College of Physicians/Surgeons of Canada)
- the College of Family Physicians of Canada (CFPC) certifies family physicians who complete an accredited residency program and pass the Certification Examination in Family Medicine
- the RCPSC and CFPC are responsible for monitoring ongoing continuing medical education (CME) and professional development



Certification by the LMCC plus either the RCPSC or CFPC is a minimum requirement for licensure by most provincial licensing authorities.

## Role of Professional Associations

- membership in a provincial or national association is voluntary
- provincial medical associations represent the economic and professional interests of doctors
- the Canadian Medical Association (CMA) is a national association that provides leadership to doctors and advocates for access to high quality health care in Canada
- the CMA represents physician and population concerns at the national level, while the provincial medical associations negotiate fee and benefit schedules with provincial governments
- medical residents are represented nationally by the Canadian Association of Interns and Residents, and provincially by Provincial Housestaff Organizations, which uphold the economic and professional interests of residents
- medical students are represented at their universities by student societies; these bodies collectively form the Canadian Federation of Medical Students; francophone medical schools participate in the Federation of Quebec Medical Student Societies
- the Canadian Medical Protective Association (CMPA), a physician-run organization, is a voluntary insurance association that protects the integrity of member physicians by providing legal defense against allegations of malpractice or negligence and by providing risk management and educational programs, and general advice

## The US Health Care System

- the United States health care system is more market-based than the Canadian system
- it is funded and delivered by a mixture of the public, private, and voluntary sectors; private-for-profit is the prevailing method of delivery
- public funding is derived from taxes raised at both the federal and state government levels

## History

- 1850 Franklin Health Insurance Company of Massachusetts
- offers accident insurance to cover injuries acquired during railroad or steamboat travel
  - informal “sickness insurance” evolved from this to cover different injuries or diseases
- 1901 American Medical Association established as the national organization of state and local medical groups
- 1929 Baylor Plan developed
- created by Dr. Justin Ford Kimball to ensure that teachers could pay their medical bills
  - teachers pay 50 cents/month in exchange for guarantee of medical services for 21 d
- 1930s More hospitals adopt medical insurance plans as per the Baylor Plan
- emergence of private, commercial, health insurance as a service of life insurance companies
- 1939 Community hospitals work together to create health care plans
- American Hospital Association (AHA) uses the term “Blue Cross” to describe health care plans that meet their standards
  - emergence of prepaid plans covering physician and surgeon services
- 1940s and 1950s
- employee benefit plans increase in number with more comprehensive health care insurance packages
  - companies compete for employees using the proposed health care plan
  - reason why workplace is currently main source of health care insurance
- 1946 Blue Shield created and represents physician sponsored health care plans
- 1954 Social Security coverage begins to include disability benefits
- 1960 Blue Cross becomes the official designation for AHA health care plans
- 1965 Medicare and Medicaid programs introduced government funded health care plans
- 1971 Blue Cross and Blue Shield merge into one company
- 1970s and 1980s
- emergence of Health Maintenance Organizations (HMOs)
  - HMOs offer managed care plans: health care packages that are provided by an HMO approved network of health care providers
- 1993 Universal health care system proposed but rejected by congress
- 1996 *Mental Health Parity Act* passed
- invoked to decrease discrimination in health care coverage for mental health illnesses
  - aggregate annual and lifetime limits for mental health services must match aggregate annual and lifetime limits for medical and surgical services
- 1996 *Health Insurance Portability and Accountability Act* passed
- Title 1: Health Care Access, Portability, and Renewability
    - provides protection of health care coverage to employees and their families if they change or lose their job
  - Title 2: Preventing Health Care Fraud and Abuse; Administrative Simplification; Medical Liability Reform
    - addresses and establishes national standards for electronic health care transactions and security and privacy of health data
- 1997 State Children’s Health Insurance Program (SCHIP) created
- states extend health coverage to uninsured children
- 1999 *Ticket to Work and Work Incentives Improvement Act*
- enables people with disabilities to be employed without affecting their Medicaid or Medicare coverage
- 2010 *Affordable Care Act*
- reform to health care to improve access to affordable health coverage and creates regulations on activities of private health insurance providers



## Health Care Expenditure and Delivery in the US

- health care spending in the US represents a large economic sector
  - health care comprises over 17.4% of the gross domestic product (GDP) (highest in the OECD), amounting to \$7960 USD per capita in 2009
  - one advantage is the widespread availability of technology – the US has 4 times as many MRI machines per capita than Canada
- the US scores poorly on some indicators of population health, with a life expectancy below the OECD average and infant mortality above the OECD average. Possible factors that account for this discrepancy are:
  - poor health of large uninsured population
  - high cost of health care administration
  - the provision of inefficient high-cost, high-intensity care
    - the higher-spending regions in the US do not provide any better quality of care, access to care, health outcomes or satisfaction with care when compared to the lower-spending regions
- the US has the highest level of obesity of all OECD nations at 34.3%; this has major implications for future health care spending



### Cost of Health Care Administration in the United States and Canada *NEJM* 2003;349:768-775

Administrative costs were estimated from data on insurance overhead, employers' costs to manage benefits, and the administrative costs of hospitals, practitioners' offices, nursing homes, and home care. In 1999, the cost of U.S. health administration was \$1,059 per capita, more than three times greater than the cost in Canada (\$307 per capita).

## Access to Health Services

- 70% of Americans under the age of 65 have private health insurance, either employer-sponsored or individually purchased; 12% receive health care through public health insurance; 18%, mainly the poor, have no health insurance
- access to publicly funded health services occurs primarily through two programs, Medicare and Medicaid, which were created by the 1965 *Social Security Act*
- other federal government-funded health programs include the Military Health Services System, the Veterans Affairs Health Services System, the Indian Health Service, and the Prison Health Service

**Table 4. Medicare and Medicaid Program Information**

	Medicare	Medicaid
<b>Eligibility</b>	People over the age of 65 People with end stage renal disease People of any age meeting the Medicare definition of disability	People who receive funds through social assistance programs Pregnant women People with developmental disabilities Low-income children through the 1997 State Children's Health Insurance Program
<b>Coverage</b>	Basic "Part A" providing inpatient hospital care, home care, limited skilled nursing facility care, and hospice care Supplemental "Part B" covers outpatient physician and clinic services, and requires payment of a further monthly fee	Basic coverage involves inpatient and outpatient hospital care, laboratory and x-ray services, skilled nursing care, home care, physician services, dental services, and family planning Financing for Medicaid is provided jointly by the federal and state governments, and program details vary greatly between states
<b>Co-payment</b>	To help pay for out-of-pocket expenditures, and to cover many of the services not insured by Medicare, the majority of Medicare beneficiaries buy supplemental private health insurance	States may impose deductibles, coinsurance, or co-payments on some Medicaid recipients for certain services Medicaid is not health insurance – coverage is unreliable as improvement in an individual's financial status can lead to a loss of Medicaid eligibility

Source: Centers for Medicare and Medicaid Services. <http://www.cms.gov>

## Health Care Reform

- Patient Protection and Affordable Care Act* and the *Health Care and Education Reconciliation Act of 2010* are federal statutes signed into law in March 2010 that include a number of new health care provisions to be implemented over 8 yr
  - expand Medicaid eligibility, provide subsidies for insurance premiums and incentives for businesses to provide health care benefits, prohibit denial of coverage/claims for pre-existing conditions, and establish health-insurance exchanges
  - costs are offset by a number of health care related taxes, including a tax penalty for citizens with no health insurance (low income persons are exempt)



# References

## Bioethics

- Bioethics for Clinicians Series. CMAJ.  
CMA Code of Ethics, Canadian Medical Association (Internet). Available from: <http://www.cma.ca>.  
Etchells E, Sharpe G, Elliott C, Singer PA. Bioethics for clinicians. CMAJ 1996;155:657-661.  
Hébert P. Doing right: a practical guide to ethics for physicians and medical trainees, 2nd ed. Toronto: Oxford University Press, 2009.  
Hébert PC, Hoffmaster B, Glass KC, Singer PA. Bioethics for clinicians. CMAJ 1997;156:225-228.

## Governing Organizations

- Canadian Medical Association (Internet). Available from: <http://www.cma.ca>.  
Centers for Medicare and Medicaid Services (Internet). Available from: <http://www.cms.hhs.gov>.  
College of Physicians and Surgeons of Ontario (Internet). Available from: <http://www.cpso.on.ca>.  
College of Physicians and Surgeons of Ontario. CPSO policy statements (Internet). Available from: <http://www.cpso.on.ca/policies/mandatory.htm>.  
Democratic Policy Committee. Patient protection and affordable care act (Internet). Available from: [http://dpc.senate.gov/dpcdoc-sen\\_health\\_care\\_bill.cfm](http://dpc.senate.gov/dpcdoc-sen_health_care_bill.cfm).  
Ontario Medical Association. Available from: <http://www.oma.org>.  
Royal College of Physicians and Surgeons of Ontario. CanMEDS 2005 framework (Internet). Available from: [http://www.royalcollege.ca/shared/documents/canmeds/the\\_7\\_canmeds\\_roles\\_e.pdf](http://www.royalcollege.ca/shared/documents/canmeds/the_7_canmeds_roles_e.pdf).  
WHO. World Health Report 2005. Available from: <http://www.who.int/whr/en>.

## Health Care Delivery

- Baile WF, Buckman R, Lenzi R, et al. SPIKES: a six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist* 2000;5:302-311.  
Baker GR, Norton PG, Flintoft V, et al. The Canadian adverse events study: the incidence of adverse events among hospital patients in Canada. CMAJ 2004;70:1678-1686.  
Canadian Institute for Health Information. National health expenditure trends 1975 to 2009. Ottawa: CIHI, 2009.  
Collier R. Steps forward no guarantee that health targets will be met, council says. CMAJ 2011;183:e619-620.  
Devereaux PJ, Choi PT, Lacchetti C, et al. A systematic review and meta-analysis of studies comparing mortality rates of private for-profit and private not-for-profit hospitals. CMAJ 2002;166:1399-1406.  
Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 1: The content, quality, and accessibility of care. *Ann Intern Med* 2003;138:273-287.  
Fisher ES, Wennberg DE, Stukel TA, et al. The implications of regional variations in Medicare spending. Part 2: Health outcomes and satisfaction with care. *Ann Intern Med* 2003;138:288-298.  
Historical Highlights (Internet). 2012. Available from: <http://www.hhs.gov/about/hhshist.html>.  
Institute of Medicine. Care without coverage: too little, too late. Washington: The National Academies Press (Internet). 2002. Available from: <http://www.iom.edu>.  
Kirby M. The Kirby Commission: The health of Canadians – the federal role (Internet). 2002. Available from: <http://www.parl.gc.ca/37/2/parlbus/commbus/senate/Com-e/soci-e/rep-e/rep02vol6-e.htm>.  
NAMI. The mental health parity act of 1996 (Internet). 2012. Available from: [http://www.nami.org/Content/ContentGroups/E-News/1996/The\\_Mental\\_Health\\_Parity\\_Act\\_of\\_1996.htm](http://www.nami.org/Content/ContentGroups/E-News/1996/The_Mental_Health_Parity_Act_of_1996.htm).  
National Center for Health Statistics, Center for Disease Control and Prevention (Internet). Available from: <http://www.cdc.gov/nchs>.  
National Center for Health Statistics. With special feature on medical technology. Hyattsville (US). 2010.  
Naylor CD. Health care in Canada: incrementalism under fiscal duress. *Health Affairs* 1999;18:9-26.  
OECD. Health Data. 2008. Available from: <http://www.oecd.org>.  
PBS. Healthcare crisis: healthcare timeline (Internet). 2012. Available from: <http://www.pbs.org/healthcarecrisis/>.  
Romanow R. The Romanow report: Royal commission on the future of health care in Canada (Internet). 2002. Available from: [http://www.hc-sc.gc.ca/hcs-sss/alt\\_formats/hpb-dgps/pdf/hhr/romanow-eng.pdf](http://www.hc-sc.gc.ca/hcs-sss/alt_formats/hpb-dgps/pdf/hhr/romanow-eng.pdf).  
Shah CP. Public health and preventive medicine in Canada, 5th ed. Toronto: Elsevier Canada, 2003. p357-360,426.  
Stoddart G, Guyatt GH. Payments for care at private for-profit and private not-for-profit hospitals: a systematic review and meta-analysis. CMAJ 2004;170:1817-1824.  
The history of medical insurance in the United States. *Yale Journal of Medicine & Law* (Internet). 2012. Available from: <http://www.yalemedlaw.com/2009/11/the-history-of-medical-insurance-in-the-united-states/>.  
The Senate Committee on Social Affairs, Science and Technology. News release: tables its report on the review of the 2004 health accord (Internet). 2012. Available from: <http://www.parl.gc.ca/Content/SEN/Committee/411/soci/press/27mar12B-e.htm>.  
The White House. Health care that works for Americans (Internet). Available from: <http://www.whitehouse.gov/healthreform/healthcare-overview>.  
Wikipedia, the free encyclopedia. Health insurance portability and accountability act (Internet). 2012. Available from: [http://en.wikipedia.org/wiki/Health\\_Insurance\\_Portability\\_and\\_Accountability\\_Act](http://en.wikipedia.org/wiki/Health_Insurance_Portability_and_Accountability_Act).  
Woolhandler S, Campbell T, Himmelstein DU. Costs of health care administration in the United States and Canada. *NEJM* 2003;349:768-775.

## Important Acts/Charters

- Canada Health Act, 1985. R.S.C., c. C-6.  
Canadian Public Health Association and WHO. Ottawa charter for health promotion. Ottawa: Health and Welfare Canada, 1986.  
Health Care Consent Act, 1996. S.O. c. 2, Sched. A.  
Health Protection and Promotion Act, 1990. R.S.O., c.H.7; O. Reg. 559/91, amended to O. Reg. 96/03.

## Law

- Devereaux PJ, Heels-Ansdell D, Lacchetti C, et al. Canadian health law and policy. Markham: LexisNexis, 2007.  
Ferris LE, Barkun H, Carlisle J, et al. Defining the physician's duty to warn: consensus statement of Ontario's medical expert panel on duty to inform. CMAJ 1998;158:1473-1479.  
Medical Council of Canada. Objectives of the considerations of the legal, ethical and organizational aspects of the practice of medicine (Internet). 1999. Available from: <http://www.mcc.ca>.  
Ontario Medical Association. Physician privacy toolkit (Internet). 2004. Available from: <http://www.oma.org/phealth/privacymain.htm>.  
Ontario's Office of the Chief Coroner (Internet). Available from: <http://www.mpss.jus.gov.on.ca>.

## Research Ethics

- Government of Canada: Interagency advisory panel on research ethics (Internet). Available from: <http://www.pre.ethics.gc.ca/english/index.cfm>.

Gavin Hamilton and Ashwin Sankar, chapter editors

Maria Jogova and Howard Meng, associate editors

Melini Gupta, EBM editor

Dr. Isabella Devito and Dr. Diana Tamir, staff editors

<b>Anesthesia Basics</b> . . . . .	<b>2</b>	<b>Extubation</b> . . . . .	<b>17</b>
<b>Pre-Operative Assessment</b> . . . . .	<b>2</b>	<b>Post-Operative Care</b> . . . . .	<b>17</b>
History and Physical		<b>Pain Management</b> . . . . .	<b>18</b>
Pre-Operative Investigations		<b>Regional Anesthesia</b> . . . . .	<b>19</b>
Fasting Guidelines		Definition of Regional Anesthesia	
American Society of Anesthesiology (ASA)		Preparation for Regional Anesthesia	
Classification		Epidural and Spinal Anesthesia	
<b>Pre-Operative Optimization</b> . . . . .	<b>4</b>	Peripheral Nerve Blocks	
Medications		<b>Local Anesthesia</b> . . . . .	<b>21</b>
Hypertension		Local Anesthetic Agents (LA)	
Coronary Artery Disease (CAD)		Local Infiltration and Hematoma Blocks	
Endocrine Disorders		Topical Anesthetics	
Respiratory Diseases		<b>Obstetrical Anesthesia</b> . . . . .	<b>22</b>
Aspiration		<b>Pediatric Anesthesia</b> . . . . .	<b>23</b>
<b>Monitoring</b> . . . . .	<b>5</b>	<b>Uncommon Complications</b> . . . . .	<b>24</b>
<b>Induction Agents</b> . . . . .	<b>6</b>	Malignant Hyperthermia (MH)	
Intravenous Agents		Abnormal Pseudocholinesterase	
Volatile Inhalational Agents		<b>Common Medications</b> . . . . .	<b>25</b>
Muscle Relaxants and Reversing Agents		Intravenous Induction Agents	
<b>Airway Management</b> . . . . .	<b>7</b>	Opioids	
Airway Anatomy Review		Volatile Inhalational Agents	
Tracheal Intubation		Depolarizing Muscle Relaxants	
Routine Induction vs. Rapid Sequence		Non-Depolarizing Muscle Relaxants	
Induction (RSI)		Reversal Agents for Non-Depolarizing Relaxants	
Difficult Airway		Local Anesthetic Agents	
<b>Intraoperative Management</b> . . . . .	<b>10</b>	<b>Advance Cardiac Life Support</b>	
Oxygen Therapy		<b>(ACLS) Guidelines</b> . . . . .	<b>28</b>
Ventilation		<b>References</b> . . . . .	<b>30</b>
Temperature			
Heart Rate			
Blood Pressure			
Fluid Balance and Resuscitation			
IV Fluids			
Blood Products			

## Acronyms

2,3-DPG	2,3-Diphosphoglycerate	ETT	endotracheal tube	LOC	level of consciousness	PONV	post-operative nausea and vomiting
ACC	American College of Cardiology	FiO <sub>2</sub>	fraction of oxygen in inspired air	MAC	minimum alveolar concentration	PPV	positive pressure ventilation
ACh	acetylcholine	FFP	fresh frozen plasma	MAP	mean arterial pressure	RSI	rapid sequence induction
AChE	acetylcholinesterase	FRC	functional residual capacity	MH	malignant hyperthermia	SABA	short-acting β-agonist
AHA	American Heart Association	GA	general anesthetic	MS	multiple sclerosis	SCh	succinylcholine
ALS	amyotrophic lateral sclerosis	GERD	gastroesophageal reflux disease	NMJ	neuromuscular junction	SIADH	syndrome of inappropriate antidiuretic hormone
ARDS	acute respiratory distress syndrome	Hb(i)	initial hematocrit	NYHA	New York Heart Association	SNS	sympathetic nervous system
atm	atmosphere	Hb(f)	final hematocrit	OCS	oral corticosteroids	SV	stroke volume
CCS	Canadian Cardiovascular Society	Hct	hematocrit	OR	operating room	SVR	systemic vascular resistance
CK	creatine kinase	HES	hydroxyethyl starch	P <sub>a</sub> CO <sub>2</sub>	arterial partial pressure of carbon dioxide	TBW	total body water
CO	cardiac output	ICP	intracranial pressure	P <sub>a</sub> O <sub>2</sub>	arterial partial pressure of oxygen	TIVA	total intravenous anesthetic
CSF	cerebrospinal fluid	ICS	inhaled corticosteroids	PC	patient-controlled	TURP	transurethral resection of prostate
CVP	central venous pressure	IOP	intraocular pressure	PCA	patient controlled analgesia	V/Q	ventilation/perfusion
DIC	disseminated intravascular coagulopathy	LA	local anesthetic	PEEP	positive end-expiratory pressure	VT	ventricular tachycardia
DPG	diphosphoglycerate	LABA	long-acting β-agonist	PNS	parasympathetic nervous system	VTE	venous thromboembolism
ETCO <sub>2</sub>	End Tidal CO <sub>2</sub>	LES	lower esophageal sphincter				
		LMA	laryngeal mask airway				

## Anesthesia Basics

### Types of Anesthesia

- **general**
  - general anesthesia (GA)
  - total IV anesthesia (TIVA)
- **regional**
  - spinal, epidural
  - peripheral nerve block
  - IV regional
- **local**
  - local infiltration
  - topical
- **sedation**
  - monitored anesthesia care
- note that different types of anesthesia can be combined (e.g. general + regional)



#### 6 As of General Anesthesia

Anesthesia  
 Anxiolysis  
 Amnesia  
 Areflexia (muscle relaxation not always required)  
 Autonomic Stability  
 Analgesia

## Pre-Operative Assessment



- to identify the patient's medical and surgical issues
- to allow for the arrangement of further investigations, consultations and treatments for patients not yet optimized
- to plan and consent for anesthetic techniques

## History and Physical

### History

- indication for surgery
- surgical/anesthetic Hx: previous anesthetics/complications, previous intubations, medications, drug allergies
- PMHx:
  - CNS: seizures, strokes, raised ICP, spinal disease
  - CVS: CAD, MI, CHF, HTN, valvular disease, dysrhythmias, peripheral vascular disease (PVD), conditions requiring endocarditis prophylaxis, exercise tolerance, CCS class, NYHA class (see [Cardiology and Cardiovascular Surgery](#), C31 for NYHA classification)
  - respiratory: smoking, asthma, COPD, recent upper respiratory tract infection, sleep apnea
  - GI: GERD, liver disease
  - renal: insufficiency, dialysis, chronic kidney disease
  - hematologic: anemia, coagulopathies, blood dyscrasias
  - MSK: conditions associated with difficult intubations – arthritides (e.g. rheumatoid arthritis), cervical tumours, cervical infections/abscesses, trauma to cervical spine, previous cervical spine surgery, Down syndrome, scleroderma, obesity, conditions affecting neuromuscular junction (e.g. myasthenia gravis)
  - endocrine: diabetes, thyroid disorders, adrenal disorders
  - other: morbid obesity, pregnancy, ethanol/other drug use
- FHx: malignant hyperthermia, atypical cholinesterase (pseudocholinesterase), other abnormal drug/anesthetic reactions



### Physical Examination

- examination of organ systems
  - focused physical exam of the CNS, CVS and respiratory systems
  - general assessment of nutrition, hydration and mental status
  - pre-existing motor and sensory deficits
- oropharynx and airway assessment to determine the likelihood of difficult intubation
  - no single test is specific or sensitive – all aid in determining the ease of intubation
  - ability to assume “sniffing position” – upper cervical spine extension, lower cervical spine flexion, previous cervical spine surgery
  - Mallampati classification (Figure 1)
  - “3-2-1 rule”
    - ♦ thyromental distance (the distance of the lower mandible in the midline from the mentum to the thyroid notch); <3 finger breadths (<6 cm) is associated with difficult intubation
    - ♦ mouth opening (<2 finger breadths is associated with difficult intubation)
    - ♦ anterior jaw subluxation (<1 finger breadth is associated with difficult intubation)
  - tongue size
  - dentition, dental appliances/prosthetic caps – must inform patients of the rare possibility of damage
  - nasal passage patency (if planning nasotracheal intubation)
- examination of anatomical sites relevant to lines and blocks
  - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
  - sites for IV, central venous pressure (CVP) and pulmonary artery (PA) catheters

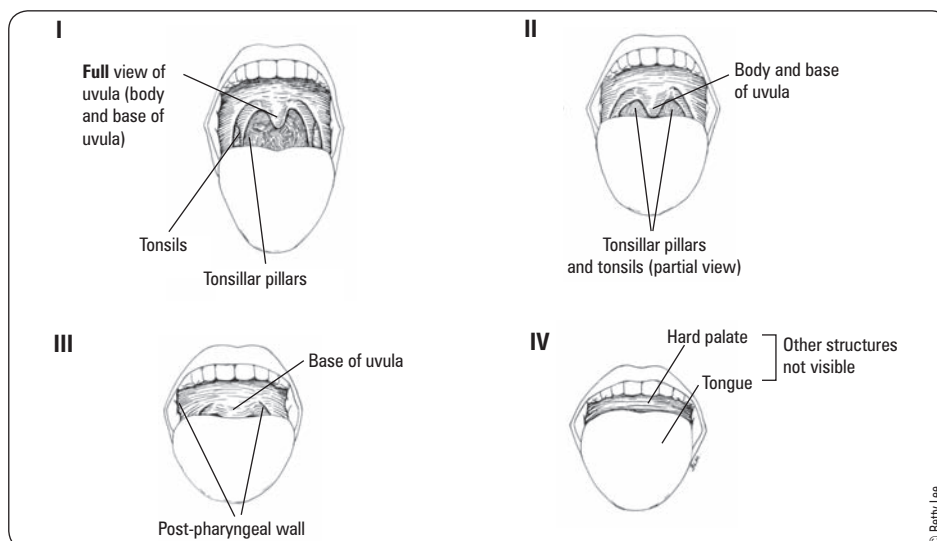


Figure 1. Mallampati classification of oral opening



#### Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality

Anesth 2005;102:257-268

**Study:** Case-control study of patients undergoing anesthesia.

**Patients:** 807 cases and 883 controls were analyzed among a cohort of 869,483 patients undergoing anesthesia between 1995-1997. Cases were defined as patients who either remained comatose or died within 24 h of receiving anesthesia. Controls were defined as patients who neither remained comatose nor died within 24 h of receiving anesthesia.

**Intervention:** General, regional or combined anesthesia to patients undergoing a surgical procedure.

**Main Outcome:** Coma or death within 24 h of receiving anesthesia.

**Results:** The incidence of 24 h postoperative death was 8.8 per 10,000 anesthetics (95% CI, 8.2-9.5) and the incidence of coma was 0.5 (95% CI, 0.3-0.6). Anesthesia management risk factors that were associated with a decreased risk of morbidity and mortality were equipment check with protocol and documentation, directly available anesthesiologist with no change during anesthesia, 2 persons present at emergence of anesthesia, reversal of muscle relaxation and postoperative pain medication.

## Pre-Operative Investigations

Table 1. Suggested Indications for Specific Investigations in the Pre-Operative Period

Test	Indications
<b>CBC</b>	Major surgery requiring group and screen or cross and match; chronic cardiovascular, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression; patient less than 1 yr of age
<b>Sickle cell screen</b>	Genetically predisposed patient (hemoglobin electrophoresis if screen is positive)
<b>INR, aPTT</b>	Anticoagulant therapy, bleeding diathesis, liver disease
<b>Electrolytes and creatinine</b>	Hypertension, renal disease, diabetes, pituitary or adrenal disease; digoxin, diuretic or other drug therapies affecting electrolytes
<b>Fasting glucose level</b>	Diabetes (repeat on day of surgery)
<b>Pregnancy (β-HCG)</b>	Women who may be pregnant
<b>ECG</b>	Heart disease, diabetes, other risk factors for cardiac disease; subarachnoid or intracranial hemorrhage, cerebrovascular accident, head trauma
<b>Chest radiograph</b>	Cardiac or pulmonary disease, malignancy

Guidelines to the Practice of Anesthesia Revised Edition 2013. Supplement to the Canadian Journal of Anesthesia, Vol 60, Dec. 2013. Reproduced with permission © Canadian Anesthesiologists' Society

## Fasting Guidelines

### Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists' Society)

- **8 hours** after a meal that includes meat, fried or fatty foods
- **6 hours** after a light meal (such as toast or crackers) or after ingestion of infant formula or nonhuman milk
- **4 hours** after ingestion of breast milk or Jello
- **2 hours** after clear fluids (water, black coffee, tea, carbonated beverages, juice without pulp)

## American Society of Anesthesiology (ASA) Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- **ASA 1:** a healthy, fit patient
- **ASA 2:** a patient with mild systemic disease
  - e.g. controlled type 2 diabetes mellitus (DM), controlled essential HTN, obesity, smoker
- **ASA 3:** a patient with severe systemic disease that limits activity
  - e.g. stable CAD, COPD, DM, obesity
- **ASA 4:** a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure

- **ASA 5:** a moribund patient not expected to survive 24 h without surgery
  - e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- **ASA 6:** declared brain dead, a patient whose organs are being removed for donation purposes
- for emergency operations, add the letter **E** after classification (e.g. ASA 3E)

## Pre-Operative Optimization

- in general, any fluid and/or electrolyte imbalance should be corrected prior to elective surgery

## Medications

- pay particular attention to cardiac and respiratory medications, opioids and drugs with many side effects and interactions
- **pre-operative medications to consider**
  - prophylaxis
    - ♦ risk of GE reflux: sodium citrate 30 mL PO or ranitidine 150-300 mg PO or metoclopramide 10 mg PO 30 min to 1 h pre-op
    - ♦ risk of infective endocarditis, GI/GU interventions: antibiotics
    - ♦ risk of adrenal suppression: steroid coverage
    - ♦ consider benzodiazepines for the anxious patient
    - ♦ bronchodilators (COPD, asthma)
    - ♦ nitroglycerin and  $\beta$ -blockers (CAD risk factors)
- **pre-operative medications to stop**
  - oral hypoglycemics: stop on morning of surgery
  - antidepressants: stop on morning of surgery
  - ACE inhibitors and angiotension receptor blockers: stop on morning of surgery
  - warfarin (consider bridging with heparin), anti-platelet agents (e.g. clopidogrel)
    - ♦ discuss peri-operative use of ASA, NSAIDs with surgeon
- **pre-operative medication to adjust**
  - insulin (consider insulin/dextrose infusion), prednisone, bronchodilators

## Hypertension

- mild to moderate HTN is not an independent risk factor for peri-operative cardiovascular complications
- target sBP <180 mmHg, dBP <110 mmHg
- assess for end-organ damage and treat accordingly

## Coronary Artery Disease (CAD)

- ACC/AHA Guidelines (2007) recommend postponing elective surgery 4-6 wk following an MI
- this period carries an increased risk of reinfarction/death
  - <3 mo after MI – 37% patients may reinfarct
  - 3-6 mo after MI – 15%
  - >6 mo after MI – risk remains constant at 5%
- if operative procedure is essential and cannot be delayed, invasive intra- and post-operative ICU monitoring reduces the risk to 6%, 2% and 1% respectively for the above time periods
- mortality with peri-operative MI is 20-50%
- initiation of peri-operative  $\beta$ -blockade previously advocated; currently, some recent studies have suggested an increased risk of stroke
  - $\beta$ -blockade should be continued if already started
  - initiate  $\beta$ -blockade if inducible ischemia, CAD or multiple cardiac risk factors and undergoing high risk surgery
  - consider initiating and optimizing  $\beta$ -blockade if CAD or multiple cardiac risk factors and undergoing intermediate risk surgery

## Endocrine Disorders

- diabetes mellitus
  - hypoglycemia
    - ♦ caused by drugs and surgical stresses and masked by anesthesia
    - ♦ appropriate use of dextrose/insulin infusion and blood glucose monitoring
  - end organ damage: be aware of damage to CVS, renal and nervous systems, including autonomic neuropathy



### Effects of Extended-Release Metoprolol Succinate in Patients Undergoing Non-Cardiac Surgery (POISE trial): A Randomized Controlled Trial

*Lancet* 2008;371:1839-1847

**Purpose:** To investigate the role of  $\beta$ -blockers (metoprolol) peri-operatively in patients with known vascular disease undergoing non-cardiac surgery.

**Methods:** Patients from 190 centres in 23 countries were eligible if they were age >45, undergoing non-cardiac surgery and were known to have significant vascular disease. Patients were randomized to either the metoprolol group or placebo. Participants received metoprolol (or placebo) 100 mg 2-4 h prior to surgery, 6 h after surgery, and then 20 mg daily for 30 d. The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest. Analysis was by intention to treat.

**Results:** 8351 patients were recruited into the study, with 8331 completing the 30 d course. Use of metoprolol was found to significantly reduce the risk of cardiovascular death, non-fatal MI or non-fatal cardiac arrest vs. placebo (hazard ratio 0.84,  $p < 0.05$ ) but significantly increased the rate of stroke (hazard ratio 2.17,  $p < 0.01$ ) and overall risk of death (hazard ratio 1.33,  $p < 0.05$ ).

**Conclusion:** Use of peri-operative  $\beta$ -blockers (metoprolol) in patients with known vascular disease provides both risks and benefits, and these must be considered for each patient individually.

- hyperthyroidism
  - can experience sudden release of thyroid hormone (thyroid storm)
  - treatment:  $\beta$ -blockers and pre-op prophylaxis
- adrenocortical insufficiency (e.g. Addison's, exogenous steroid use)
  - consider steroid coverage if steroid use of >1 wk in past 6 mo

## Respiratory Diseases

- smoking
  - adverse effects: altered mucus secretion and clearance, decreased small airway caliber and altered immune response
  - abstain at least 8 wk pre-op if possible
  - if unable, abstaining even 24 h pre-op has shown benefit
- asthma
  - increased risk of bronchospasm from intubation, delivery of desflurane
  - pre-op management depends on degree of baseline asthma control
  - pre-op SABA, LABA, ICS, OCS may be used up to 1 wk pre-op to achieve adequate asthma control
  - avoid non-selective  $\beta$ -blockers; cardioselective  $\beta$ -blockers (e.g. metoprolol, atenolol) do not increase risk of bronchospasm in the short term
  - cancel/delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
- COPD
  - anesthesia, surgery and analgesia predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation and respiratory failure
  - cancel/delay elective surgery for acute exacerbation
  - optimize with bronchodilators  $\pm$  ICS  $\pm$  antibiotics



### $\beta$ -blockers

- $\beta_1$  receptors are located primarily in the heart and kidneys
- $\beta_2$  receptors are located in the lungs
- Non-selective  $\beta$ -blockers block  $\beta_1$  and  $\beta_2$  receptors. Caution is required with non-selective  $\beta$ -blockers, particularly in patients with respiratory conditions where  $\beta_2$  blockade can result in airway reactivity

## Aspiration

- conditions with increased risk of aspiration:
  - decreased LOC
  - trauma
  - meal within 8 h
  - suspected sphincter incompetence (GERD, hiatus hernia, nasogastric tube)
  - increased abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
- management: reduce gastric volume and acidity, delay inhibiting airway reflexes, employ rapid sequence induction if increased risk (see *Rapid Sequence Induction*, A9)
- increased risk with laryngeal mask instead of endotracheal tube (ETT)

## Monitoring

### Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

- an anesthetist present: "the only indispensable monitor"
- a completed pre-anesthetic checklist: including ASA class, NPO policy, Hx and investigations
- a peri-operative anesthetic record: HR and BP every 5 min, dose and route of drugs and fluids
- continuous monitoring: see *Routine Monitors* below

### Routine Monitors for All Cases

- **pulse oximeter**, apparatus to measure BP, **electrocardiography**, **capnography** for general anesthesia and sedation (Ramsey Sedation Scale 4-6), agent-specific anesthetic gas monitor when inhalation anesthetic agents are used
- the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometer

### Elements to Monitor

- anesthetic depth
  - inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing or sweating
  - excessive: hypotension, bradycardia
- oxygenation: pulse oximetry, fraction of inspired  $O_2$  ( $FiO_2$ )
- ventilation: verify correct position of ETT, chest excursions, breath sounds,  $ET_{CO_2}$  analysis, end tidal inhaled anesthesia analysis
- circulation: pulse, heart sounds, BP, telemetry, oximetry, CVP, pulmonary capillary wedge pressure
- temperature: temperature probe



### Pre-Anesthetic Checklist

#### SAMMM

**Suction:** connected and working  
**Airways:** laryngoscope and blades, ETT, syringe, stylet, oral and nasal airways, tape, bag and mask  
**Machine:** connected, pressures okay, all meters functioning, vaporizers full  
**Monitors:** available, connected and working  
**Medications:** IV fluids and kit ready, emergency medicines in correct location and accessible



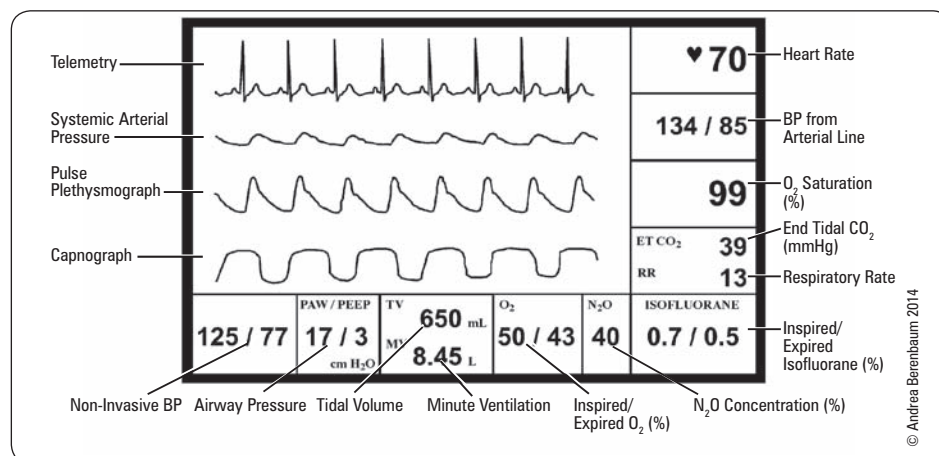


Figure 2. Typical anesthesia monitor

## Induction Agents

- induction may be achieved with intravenous agents, volatile agents or both

### Intravenous Agents

- see Table 12, A25
- IV induction agents include a selection of non-opioid drugs used to provide amnesia and blunt reflexes
- these are initially used to draw the patient into the maintenance phase of general anesthesia rapidly, smoothly and with little adverse effects
  - e.g. propofol, sodium thiopental (not available in North America) or ketamine
  - a continuous propofol infusion may also be used for the maintenance phase of GA

### Volatile Inhalational Agents

- see Table 15, A26
- general concepts of volatile agents are discussed below
  - e.g. sevoflurane, desflurane, isoflurane, enflurane, halothane and nitrous oxide

#### MAC (minimum alveolar concentration)

- definition: the alveolar concentration of an agent at one atmosphere (atm) of pressure that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- often 1.2-1.3 times MAC will ablate response to stimuli in the general population
- potency of inhalational agents is compared using MAC
- MAC values are roughly additive when mixing N<sub>2</sub>O with another volatile agent (i.e. 0.5 MAC of a potent agent + 0.5 MAC of N<sub>2</sub>O = 1 MAC of potent agent; however, this only applies to movement, not other effects such as BP changes and does not hold over the entire N<sub>2</sub>O dose range)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation, generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli, generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command, usually 0.3-0.4 of the usual MAC value

Table 2. Ramsay Sedation Scale

Value	Description	Test to Follow
1	Awake: Patient is anxious and agitated, or restless, or both	Observe the patient
2	Awake: Patient is co-operative, orientated, and tranquil	Observe the patient. Does patient make eye contact and respond to commands?
3	Awake: Patient responds to commands only	Talk to the patient. Does patient make eye contact and respond to commands?
4	Asleep: Patient reacts with a brisk response to a light glabellar tap or a loud auditory stimulus	Physically stimulate the patient by shaking the shoulder while speaking loudly. Does patient respond within 10 s?
5	Asleep: Patient reacts with a sluggish response to a light glabellar tap or a loud auditory stimulus	Physically stimulate the patient by shaking the shoulder while speaking loudly. Does patient respond after 10 s?
6	Asleep: Patient does not respond to pain	Use painful stimuli. No response

Guidelines to the Practice of Anesthesia Revised Edition 2013. Supplement to the Canadian Journal of Anesthesia, Vol 60, Dec. 2013. Reproduced with permission © Canadian Anesthesiologists' Society



#### Determinants of Speed of Onset of Volatile Anesthetics

- Solubility:** decrease solubility → increase rate of induction
- Cardiac output (CO):** as CO increases, anesthetic uptake to blood increases and alveolar gas concentration decreases, thus delaying induction
- Partial pressure difference between alveolar and venous blood:** increase gradient → decrease rate of induction
- Inspired gas concentration:** increase inspired concentration → increase rate of induction
- Alveolar ventilation:** increase alveolar ventilation → increase rate of induction
- Second gas effect:** when 2 gases are administered together, uptake of the first gas (e.g. N<sub>2</sub>O) increases the alveolar concentration of the second gas (e.g. desflurane), increasing rate of induction



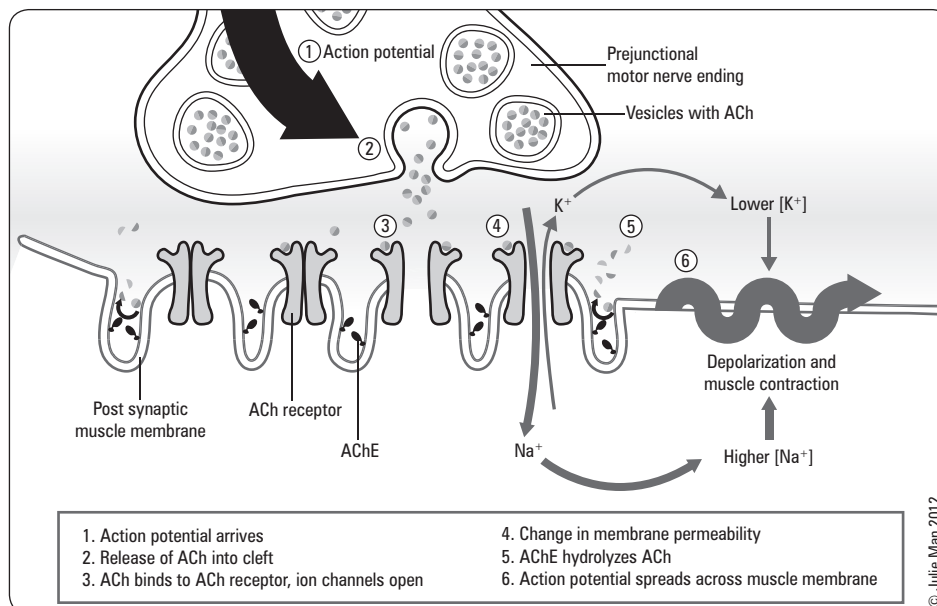
#### Solubility of Volatile Anesthetics in Blood Least Soluble to Most Soluble

Nitrous oxide < desflurane < sevoflurane < isoflurane < halothane



## Muscle Relaxants and Reversing Agents

- see Tables 16 and 17, A27; Table 18, A28
- depolarizing muscle relaxants: succinylcholine (SCh)
- non-depolarizing muscle relaxants: rocuronium, mivacurium, vecuronium, cisatracurium, pancuronium



**Figure 3. Anatomy and physiology of the neuromuscular junction (NMJ)**

### Muscle Relaxants

- never use without adequate preparation and equipment to maintain airway and ventilation
- muscle relaxation produces the following desired effects:
  1. facilitates intubation
  2. assists with mechanical ventilation
  3. prevents muscle stretch reflex and decreases muscle tone
  4. allows access to the surgical field (intracavitary surgery)
- blocks nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- nerve stimulator is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade

### Reversing Agents for Non-Depolarizing Muscle Relaxants (e.g. neostigmine, pyridostigmine, edrophonium)

- reversal agents are acetylcholinesterase inhibitors
  - inhibits enzymatic degradation of ACh; increases amount of ACh at nicotinic and muscarinic receptors, displacing non-depolarizing muscle relaxant
  - administer reversal agents when there has been some recovery of blockade (i.e. muscle twitch)
- anticholinergic agents (e.g. atropine, glycopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation and increased bowel peristalsis)



#### Plasma Cholinesterase

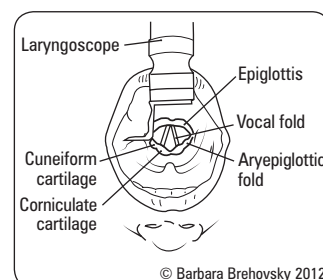
Plasma cholinesterase is produced by the liver and metabolizes SCh, ester local anesthetics and mivacurium. A prolonged duration of blockade by SCh occurs with:

- (a) decreased quantity of plasma cholinesterase, e.g. liver disease, pregnancy, malignancy, malnutrition, collagen vascular disease, hypothyroidism
- (b) abnormal quality of plasma cholinesterase, i.e. normal levels but impaired activity of enzymes, genetically inherited

## Airway Management

### Airway Anatomy Review

- normal airway: nares → nasal cavities → nasal pharynx → laryngeal pharynx → trachea
- resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- glottic opening (triangular space formed between the true vocal cords) is the narrowest segment of the laryngeal opening in adults
- when intubating, the glottic opening is used as the space through which one visualizes proper placement of the ETT
- the trachea begins at the level of the thyroid cartilage at the level of C6
- the trachea bifurcates into the right and left main bronchi at the level of T5 (approximately at the sternal angle)



**Figure 4. Landmarks for intubation**

Table 3. Methods of Supporting the Airway

	Bag and Mask	Laryngeal Mask Airway (LMA)	Endotracheal Tube (ETT)
<b>Advantages/Indications</b>	<ul style="list-style-type: none"> <li>Basic</li> <li>Non-invasive</li> <li>Readily available</li> </ul>	<ul style="list-style-type: none"> <li>Easy to insert</li> <li>Less airway trauma/irritation than ETT</li> <li>Frees up hands (vs. face mask)</li> <li>Primarily used in spontaneously ventilating patient</li> </ul>	Indications for intubation (5 Ps): <ul style="list-style-type: none"> <li>Patent airway</li> <li>Protects against aspiration</li> <li>Positive pressure ventilation</li> <li>Pulmonary toilet (suction)</li> <li>Pharmacologic administration also hemodynamic instability</li> </ul>
<b>Disadvantages/Contraindications</b>	<ul style="list-style-type: none"> <li>Risk of aspiration if decreased LOC</li> <li>Cannot ensure airway patency</li> <li>Inability to deliver precise tidal volume</li> <li>Operator fatigue</li> </ul>	<ul style="list-style-type: none"> <li>Risk of gastric aspiration</li> <li>PPV &lt;20 cm H<sub>2</sub>O needed</li> <li>Oropharyngeal/retropharyngeal pathology or foreign body</li> </ul>	<ul style="list-style-type: none"> <li>Insertion can be difficult</li> <li>Muscle relaxant usually needed</li> <li>Most invasive – see <i>Complications During Laryngoscopy and Intubation</i>, A9</li> </ul>
<b>Other</b>	<ul style="list-style-type: none"> <li>Facilitate airway patency with jaw thrust and chin lift</li> <li>Can use oropharyngeal/nasopharyngeal airway</li> </ul>	<ul style="list-style-type: none"> <li>Does NOT protect against laryngospasm or gastric aspiration</li> <li>Sizing by body weight (approx):               <ul style="list-style-type: none"> <li>40-50 kg: 3</li> <li>50-70 kg: 4</li> <li>70-100 kg: 5</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Auscultate to avoid endobronchial intubation</li> <li>Sizing (approx):               <ul style="list-style-type: none"> <li>Male: 8.0-9.0 mm</li> <li>Female: 7.0-8.0 mm</li> <li>Pediatric: (age/4) + 4 mm</li> </ul> </li> </ul>



#### Suspect Difficult Bag-Mask Ventilation with:

##### BONES

Beard  
Obesity/Obstetrics  
No teeth  
Elderly  
Sleep apnea



#### Equipment for Intubation

##### MDSOLES

Monitors  
Drugs  
Suction  
Oxygen source and self-inflating bag with oropharyngeal and nasopharyngeal airways  
Laryngoscope  
Endotracheal tubes (appropriate size and one size smaller)  
Stylet, Syringe for tube cuff inflation

## Tracheal Intubation

### Preparing for Intubation

- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare and assess for potential difficulties (see *Pre-Operative Assessment*, A2)
- ensure equipment is available and working (e.g. test ETT cuff, check laryngoscope light, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% O<sub>2</sub> for 3-5 min or for 4 vital capacity breaths
- may need to suction mouth and pharynx first

### Proper Positioning for Intubation

- “sniffing position”: flexion of lower C-spine (C5,6), i.e. bow head forward and extension of upper C-spine at atlanto (C1)-occipital joint, i.e. nose in the air
  - contraindicated in known/suspected C-spine fracture/instability
- aligns the three axes of mouth, pharynx and larynx to allow visualization from the oral cavity to the glottis (Figure 5)
- proper position for laryngoscope tip to visualize cords is in the epiglottic vallecula
- contraindicated in known/suspected C-spine fracture/instability

### Tube Insertion

- ETT insertion can incite a significant sympathetic response due to a “foreign body reflex” in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP and coughing
- a malpositioned ETT is a potential hazard for the intubated patient
  - if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
  - if too shallow, may lead to accidental extubation, vocal cord trauma or laryngeal paralysis as a result of pressure injury by the ETT cuff
- the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
  - approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women

### Confirmation of Tracheal Placement of ETT

- direct
  - visualization of ETT passing through cords
  - bronchoscopic visualization of ETT in trachea
- indirect
  - ET<sub>CO2</sub> in exhaled gas measured by capnography
  - auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
  - bilateral chest movement, condensation of water vapour in ETT visible during exhalation and no abdominal distention
  - refilling of reservoir bag during exhalation
  - CXR (rarely done): ETT tip at midpoint of thoracic inlet and carina (lateral CXR more sensitive and specific)
- esophageal intubation suspected when
  - ET<sub>CO2</sub> zero or near zero on capnograph

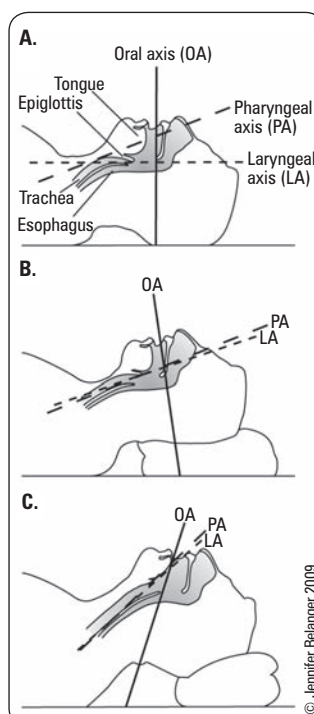


Figure 5. Anatomic considerations in laryngoscopy

- A. Neutral position  
B. C-spine flexion  
C. C-spine flexion with atlanto-occipital extension

- abnormal sounds during assisted ventilation
- impairment of chest excursion
- hypoxia/cyanosis
- presence of gastric contents in ETT
- distention of stomach/epigastrium with ventilation

### Complications During Laryngoscopy and Intubation

- dental damage
- laceration (lips, gums, tongue, pharynx, esophagus)
- laryngeal trauma
- esophageal or endobronchial intubation
- accidental extubation
- insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- laryngospasm (see *Extubation*, A17 for definition)
- bronchospasm

## Routine Induction vs. Rapid Sequence Induction (RSI)

- RSI is indicated in patients at risk of regurgitation/aspiration (see *Aspiration*, A5)

Table 4. Comparison of Routine Induction vs. RSI

Steps	Routine Induction	RSI
1. Equipment Preparation	Check equipment, drugs, suction, and monitors. Prepare an alternative laryngoscope blade and a second ETT tube one size smaller	Check equipment, drugs, suction, and monitors. Prepare an alternative laryngoscope blade and a second ETT tube one size smaller
2. Pre-Oxygenation/Denitrogenation	100% O <sub>2</sub> for 3 min or 4 vital capacity breaths	100% O <sub>2</sub> for 3 min or 4 vital capacity breaths
3. Pre-Treatment Agents	Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy	Use agent of choice to blunt physiologic responses to airway manipulation. If possible, give 3 min prior to laryngoscopy but can skip this step in an emergent situation.
3. Induction Agents	Use IV or inhalation induction agent of choice	Use fast acting induction agent of choice
4. Muscle Relaxants	Muscle relaxant of choice given after the onset of the induction agent	Fast acting muscle relaxant (e.g. SCh) given IMMEDIATELY after induction agent
5. Ventilation	Bag-mask ventilation	DO NOT bag ventilate – can increase risk of aspiration
6. Cricoid Pressure	Backwards upwards rightwards pressure (BURP) to assist visualization if indicated	Sellick maneuver, also known as cricoid pressure, to prevent regurgitation and assist in visualization (2 kg pressure with drowsiness, 3 kg with loss of consciousness)
7. Intubation	Intubate, inflate cuff, confirm ETT position	Intubate once paralyzed (~45 s after SCh given), inflate cuff, confirm ETT position. Cricoid pressure maintained until ETT cuff inflated and placement confirmed
8. Secure Machines	Secure ETT, and begin manual/machine ventilation	Secure ETT, and begin manual/machine ventilation

## Difficult Airway

- difficulties with bag-mask ventilation, supraglottic airway, endotracheal intubation, infraglottic airway or surgical airway
- algorithms exist for difficult airways (e.g. *Anesthesiology* 2003;98:3273, *Anaesthesia* 2004;59:675)
- pre-op assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures
- if difficult airway expected, consider:
  - awake intubation
  - intubating with bronchoscope, trachlight (lighted stylet), fibre optic laryngoscope, glidescope, etc.



### Medications that can be given through the ETT

#### NAVEL

Naloxone  
Atropine  
Ventolin  
Epinephrine  
Lidocaine



### Differential Diagnosis of Poor Bilateral Breath Sounds after Intubation

#### DOPE

Displaced ETT  
Obstruction  
Pneumothorax  
Esophageal intubation



### Predicting Difficult Intubation in Apparently Normal Patients

*Anesth* 2005;103:429-437

**Purpose:** To assess widely available bedside tests and widely used laryngoscopic techniques in the prediction of difficult intubations.

**Study:** Meta-analysis.

**Patients:** 35 studies encompassing 50,760 patients.

**Definitions:** Difficult intubation was defined usually as Cormack-Lehane grade of 3 or greater, but some authors reported the requirement of a special technique, multiple unsuccessful attempts, or a combination of these as the accepted standard for difficult intubation.

**Results:** The overall incidence of difficult intubation was 5.8% (95% CI, 4.5–7.5%) for the overall patient population, 6.2% (95% CI, 4.6–8.3%) for normal patients excluding obstetric and obese patients, 3.1% (95% CI, 1.7–5.5%) for obstetric patients and 15.8% (95% CI, 14.3–17.5%) for obese patients. Mallampati score: SN:49% SP:86% PLR:3.7 NLR:0.5; Thyromental distance: SN:20% SP:94% PLR:3.4 NLR:0.8; Sternomental distance: SN:62% SP:82% PLR:5.7 NLR:0.5; Mouth opening: SN:22% SP:97% PLR:4.0 NLR:0.8; Wilson risk-sum: SN:46% SP:89% PLR:5.8 NLR:0.6; Combination Mallampati and thyromental distance: SN:36% SP:87% PLR:9.9 NLR:0.6.

**Conclusions:** A combination of the Mallampati score and thyromental distance is the most accurate at predicting difficult intubation. The PLR (9.9) is supportive of the test as a good predictor of difficult intubation.

**PLR:** Positive likelihood ratio; **NLR:** Negative likelihood ratio; **SN:** Sensitivity; **SP:** Specificity

- if intubation unsuccessful after induction:
  1. CALL FOR HELP
  2. ventilate with 100% O<sub>2</sub> via bag and mask
  3. consider returning to spontaneous ventilation and/or waking patient
- if bag and mask ventilation inadequate:
  1. CALL FOR HELP
  2. attempt ventilation with oral airway
  3. consider/attempt LMA
  4. emergency invasive airway access (e.g. rigid bronchoscope, cricothyrotomy or tracheostomy)

## Intraoperative Management



### Oxygen Therapy

- in general, the goal of oxygen therapy is to maintain oxygen saturation (SaO<sub>2</sub>) >90%
- below an SaO<sub>2</sub> of 90%, a small decrease in saturation corresponds to a large drop in PaO<sub>2</sub>
- in intubated patients, oxygen is delivered via the ETT
- in patients not intubated, there are many oxygen delivery systems available; the choice depends on oxygen requirements (FiO<sub>2</sub>) and the degree to which precise control of delivery is needed
- cyanosis can be detected at SaO<sub>2</sub> <85%, frank cyanosis at SaO<sub>2</sub> = 67%

#### Low Flow Systems

- acceptable if tidal volume 300-700 mL, respiratory rate (RR) <25, consistent ventilation pattern
- provide O<sub>2</sub> at flows between 0-10 L/min
- dilution of oxygen with room air results in a decrease in FiO<sub>2</sub>
- an increase in minute ventilation (tidal volume x RR) results in a decrease in FiO<sub>2</sub>
- e.g. nasal canula (prong)
  - well tolerated if flow rates <5-6 L/min; drying of nasal mucosa at higher flows
  - nasopharynx acts as an anatomic reservoir that collects O<sub>2</sub>
  - delivered oxygen concentration (FiO<sub>2</sub>) can be estimated by adding 4% for every additional litre of O<sub>2</sub> delivered (e.g. at normal tidal volume and RR, flow rate of 1-6 L/min equates to FiO<sub>2</sub> of 24-44%)

#### Reservoir Systems

- use a volume reservoir to accumulate oxygen during exhalation thus increasing the amount of oxygen available for the next breath
- simple face mask (Hudson face mask)
  - covers patient's nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore O<sub>2</sub> tubing at a rate of at least 6 L/min to ensure that exhaled CO<sub>2</sub> is flushed through the exhalation ports and not rebreathed
  - FiO<sub>2</sub> of 55% can be achieved at O<sub>2</sub> flow rates of 10 L/min
- non-rebreather mask
  - reservoir bag and a series of one-way valves direct gas flow from the bag on inhalation and allow release of expired gases on exhalation, thus allowing for oxygen accumulation during intubation
  - O<sub>2</sub> flow rates of 10-15 L/min are needed to maintain the reservoir bag inflation and should deliver FiO<sub>2</sub> >80%

#### High Flow Systems

- generates flows of up to 50-60 L/min
- meets/exceeds patient's inspiratory flow requirement
- delivers consistent and predictable concentration of O<sub>2</sub>
- Venturi mask
  - delivers specific percentages of oxygen by varying the size of air entrainment
  - port determines the oxygen concentration (i.e. can vary to achieve 24%, 28%, 35%, 50%)
  - enables control of gas humidity
- Puritan mask
  - delivers the highest level of humidified oxygen

## Ventilation

- in patients given muscle relaxants, ventilation is maintained with PPV
- if no muscle relaxant is given, patients may have sufficient spontaneous respirations to maintain ventilation or assisted/controlled ventilation can be used
- other indications for mechanical ventilation:
  - apnea
  - hypoventilation
  - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
  - required hyperventilation (to lower ICP)

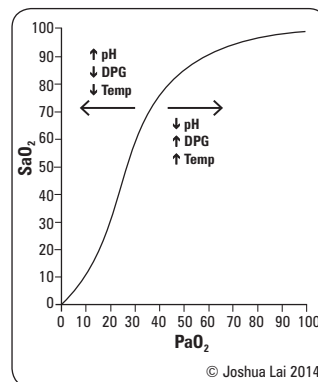


Figure 6. HbO<sub>2</sub> saturation curve



#### Alveolar O<sub>2</sub> Gas Equation

$$PAO_2 = FiO_2 (P_{atm} - P_{H_2O}) - (PaCO_2/RQ)$$

Where respiratory quotient (RQ) = 0.8



#### Arterial O<sub>2</sub> Content

$$CaO_2 = (SaO_2)(Hb)(1.34) + (PaO_2)(0.003)$$

CaO<sub>2</sub> = arterial O<sub>2</sub> content

SaO<sub>2</sub> = % hemoglobin saturation

PaO<sub>2</sub> = arterial O<sub>2</sub> pressure

RQ = respiratory quotient

- deliver positive end expiratory pressure (PEEP)
- increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation:
  - decreased CO<sub>2</sub> due to hyperventilation
  - decreased BP due to decreased venous return from increased intrathoracic pressure
  - alkalemia with over correction of chronic hypercarbia
  - nosocomial pneumonia/bronchitis
- see [Respirology](#), R26 for ventilatory modes

### Causes of Hypocapnea (decreased CO<sub>2</sub>)

- hyperventilation
- hypothermia (decreased metabolic rate)
- decreased pulmonary blood flow (e.g. decreased cardiac output)
- incorrect placement of sampling catheter
- inadequate sampling volume
- V/Q mismatch
  - pulmonary thromboembolism
  - incipient pulmonary edema
  - air embolism

### Causes of Hypercapnea (increased CO<sub>2</sub>)

- hypoventilation
- hyperthermia
- improved pulmonary blood flow after resuscitation or hypotension
- low bicarbonate
- water in capnography device
- anesthetic breathing circuit error
  - inadequate fresh gas flow
  - rebreathing
  - exhausted soda lime
  - faulty circuit absorber valves



#### Causes of Intraoperative Hypoxia

**Inadequate oxygen supply:** e.g. breathing system disconnection, obstructed or malpositioned ETT, leaks in the anesthetic machine, loss of oxygen supply.

#### Hypoventilation

**Ventilation-perfusion inequalities:** e.g. atelectasis, pneumonia, pulmonary edema, pneumothorax.

**Reduction in oxygen carrying capacity:** e.g. anemia, carbon monoxide poisoning, methemoglobinemia, hemoglobinopathy.

**Leftward shift of the hemoglobin-oxygen saturation curve:** e.g. hypothermia, decreased 2,3-DPG, alkalosis, hypocarbia, carbon monoxide poisoning.

#### Right-to-left cardiac shunt



#### Hypothermia (32°-35.9°C) Impact on Outcomes

**Increased** risk of wound infections due to impaired immune function.

**Increases** the period of hospitalization by delaying healing.

**Reduces** platelet function and impairs activation of coagulation cascade increasing blood loss and transfusion requirements.

**Triplies** the incidence of VT and morbid cardiac events.

**Decreases** the metabolism of anesthetic agents prolonging post-op recovery.

## Temperature

### Causes of Hypothermia (<36.0°C)

- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
  - OR environment (cold room, IV fluids, instruments)
  - open wound
- prevent with inflated warming blanket and warmed IV fluids (if giving platelet transfusion, put through a line that does not go through warmer because warmer distorts viability of platelets)

### Causes of Hyperthermia (>37.5-38.3°C)

- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- malignant hyperthermia (see *Uncommon Complications*, A24)
- over-zealous warming efforts

## Heart Rate

### Cardiac Arrest

- pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-shockable rhythms
  - shockable: ventricular fibrillation (VF) and ventricular tachycardia (VT)
  - non-shockable: asystole and pulseless electrical activity (PEA)
- for VF/VT, key to survival is good early CPR and defibrillation
- for asystole/PEA, key to survival is good early CPR and exclude all reversible causes
- reversible causes of PEA arrest (5 Hs and 5 Ts):
  - 5 Hs: hypothermia, hypovolemia, hypoxia, hydrogen ions (acidosis), hypo/hyperkalemia
  - 5 Ts: tamponade (cardiac), thrombosis (pulmonary), thrombosis (coronary), tension pneumothorax, toxins (overdose/poisoning)
- for management of cardiac arrest, see *ACLS Guidelines* (Figure 13), A28

### Intraoperative Tachycardia

- tachycardia = HR >150 bpm; divided into narrow complex supraventricular tachycardias (SVT) or wide complex tachycardias
- SVT: sinus tachycardia, atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
- wide complex tachycardia: VT, SVT with aberrant conduction



- causes of sinus tachycardia:
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis
  - drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium)
  - Addisonian crisis, hypoglycemia, transfusion reaction, malignant hyperthermia
- for management of tachycardia, see *ACLS Guidelines* (Figure 14), A29

### Intraoperative Bradycardia

- bradycardia = HR <50 bpm; most concerning are 2nd degree (Type 2 Mobitz) and 3rd degree heart block, which can both degenerate into asystole
- causes of sinus bradycardia:
  - increased parasympathetic tone vs. decreased sympathetic tone
  - must rule out hypoxemia
  - arrhythmias (see [Cardiology and Cardiovascular Surgery](#), C12)
  - baroreceptor reflex due to increased ICP or increased BP
  - vagal reflex (oculocardiac reflex, carotid sinus reflex, airway manipulation)
  - drugs (e.g. SCH, opioids, edrophonium, neostigmine, halothane, digoxin,  $\beta$ -blockers)
  - high spinal/epidural anesthesia
- for management of bradycardia, see *ACLS Guidelines* (Figure 15), A29



### Intraoperative Shock

**SHOCKED**  
 Sepsis or Spinal shock  
 Hypovolemic/Hemorrhagic  
 Obstructive  
 Cardiogenic  
 anaphylactic  
 Extra/other  
 Drugs



$BP = CO \times SVR$ , where  $CO = SV \times HR$

SV is a function of preload, afterload, and contractility



## Blood Pressure

### Causes of Intraoperative Hypotension/Shock (sBP <90 mmHg or MAP <60 mmHg)

- a) hypovolemic/hemorrhagic shock
- most common form of shock, due to blood loss or dehydration

**Table 5. Assessment of Hemorrhagic Shock**

	Class I	Class II	Class III	Class IV
Percentage blood loss	0-15%	15-30%	30-40%	>40%
Percentage TBW loss	0-3%	3-6%	6-9%	>9%
Heart rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Treatment	Rapid infusion of 1-2 L of crystalloid (e.g. Ringer's lactate), maintenance fluids	Rapid infusion of 2 L of crystalloid and re-evaluate	Rapid infusion of 2 L of crystalloid, replace losses with crystalloid (1:3) or pRBCs, colloid (1:1)	Rapid infusion of 2 L of crystalloid, replace losses with crystalloid (1:3) or pRBCs, colloid (1:1)
Note			Goal is to maintain urine output at >0.5 mL/kg/h	Goal is to maintain urine output at >0.5 mL/kg/h

- b) obstructive shock
- obstruction of blood into or out of the heart
  - increased JVP, distended neck veins, increased systemic vascular resistance, insufficient cardiac output (CO)
  - e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism
- c) cardiogenic shock
- myocardial dysfunction
  - increased JVP, distended neck veins, increased systemic vascular resistance, decreased CO
  - e.g. dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction
- d) septic shock
- see [Infectious Diseases](#), ID22
  - bacterial, viral, fungal, endotoxins/mediators cause vasodilation and capillary leakage
  - associated with contamination of open wounds, intestinal injury or penetrating trauma
  - fever, decreased JVP, wide pulse pressure, increased CO, increased HR, decreased systemic vascular resistance  $\pm$  pressors
  - initial treatment: antibiotics, volume expansion
- e) spinal/neurogenic shock
- decreased sympathetic tone
  - hypotension without tachycardia or peripheral vasoconstriction (warm skin)
- f) anaphylactic shock
- see [Emergency Medicine](#), ER30
  - acute/subacute generalized allergic reaction due to an inappropriate or excessive immune response (type I hypersensitivity)

- treatment of anaphylactic shock:
  - ♦ moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
    - epinephrine (1:1000) 0.3-0.5 mg SC
    - antihistamines: diphenhydramine (Benadryl®) 25-50 mg IM
    - salbutamol (Ventolin®) 1 cc via nebulizer
  - ♦ severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
    - ABCs, may need ETT due to airway edema
    - epinephrine (1:1000) 0.1-0.3 mg IV (or via ETT if no IV access) to start, repeat as needed
    - antihistamines: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg)
    - steroids: hydrocortisone (Solucortef®) 100 mg IV (~1.5 mg/kg) or methylprednisolone (Solumedrol®) 1 mg/kg IV q6h x 24 h
    - large volumes of crystalloid may be required

## g) drugs

- vasodilators, high spinal anesthetic interfering with sympathetic outflow

## h) other

- transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aorticaval syndrome
- see [Hematology](#), H52 and [Endocrinology](#), E35, E22, E26

**Causes of Intraoperative Hypertension**

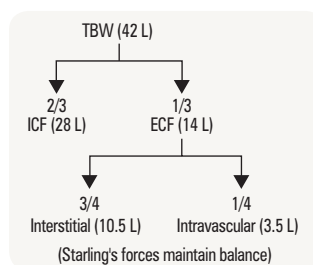
- inadequate anesthesia causing pain and anxiety
- pre-existing HTN, coarctation or preeclampsia
- hypoxemia/hypercarbia
- hypervolemia
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine)
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome (see [Psychiatry](#), PS43), thyroid storm, pheochromocytoma (see [Endocrinology](#), E25, E36)

**Fluid Balance and Resuscitation**

- total requirement = maintenance + deficit + ongoing loss
- in surgical settings this formula must take into account multiple factors including pre-operative fasting/decreased fluid intake, increased losses during or before surgery, fluid shifting during surgery, fluids given with blood products and medications

**What is the Maintenance?**

- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (beware of renal failure)
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres and CHF
- 4:2:1 rule to calculate maintenance requirements (applies to crystalloids only)
  - 4 mL/kg/h first 10 kg
  - 2 mL/kg/h second 10 kg
  - 1 mL/kg/h for remaining weight >20 kg
- maintenance electrolytes
  - Na<sup>+</sup>: 3 mEq/kg/d
  - K<sup>+</sup>: 1 mEq/kg/d
- e.g. 50 kg patient maintenance requirements
  - fluid = 40 + 20 + 30 = 90 mL/h = 2160 mL/d = 2.16 L/d
  - Na<sup>+</sup> = 150 mEq/d (therefore 150 mEq / 2.16 L/d ≈ 69 mEq/L)
  - K<sup>+</sup> = 50 mEq/d (therefore 50 mEq / 2.16 L/d ≈ 23 mEq/L)
- above patient's requirements roughly met with 2/3 D5W, 1/3 NS
  - e.g. 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per litre



**Figure 7. Total body water division in a 70 kg adult**

**What is the Deficit?**

- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total Na<sup>+</sup> content determines ECF volume; [Na<sup>+</sup>] determines ICF volume
- hypovolemia due to volume contraction
  - extra-renal Na<sup>+</sup> loss
    - ♦ GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - ♦ skin/resp: insensible losses (fever), sweating, burns
    - ♦ vascular: hemorrhage



- renal Na<sup>+</sup> and H<sub>2</sub>O loss
  - ♦ diuretics
  - ♦ osmotic diuresis
  - ♦ hypoaldosteronism
  - ♦ salt-wasting nephropathies
- renal H<sub>2</sub>O loss
  - ♦ diabetes insipidus (central or nephrogenic)
- hypovolemia with normal or expanded ECF volume
  - ♦ decreased CO
  - ♦ redistribution
    - hypoalbuminemia: cirrhosis, nephrotic syndrome
    - capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
- replace water and electrolytes as determined by patient's needs
- with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

**Table 6. Signs and Symptoms of Dehydration**

Percentage of Body Water Loss	Severity	Signs and Symptoms
3%	Mild	Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating
6%	Moderate	Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemoconcentration, apathy
9%	Severe	Profound oliguria or anuria and compromised CNS function with or without altered sensorium

**What are the Ongoing Losses?**

- tubes
  - Foley catheter, NG, surgical drains
- third spacing (other than ECF, ICF)
  - pleura, GI, retroperitoneal, peritoneal
  - evaporation via exposed viscera, burns
- blood loss
- ongoing loss due to surgical exposure and evaporative losses

**IV Fluids**

- replacement fluids include crystalloid and colloid solutions
- IV fluids improve perfusion but NOT O<sub>2</sub> carrying capacity of blood

**Crystalloid Infusion**

- salt-containing solutions that distribute within ECF
- maintain euolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement). Controversy surrounds this as an initial vs. maximal replacement target
- if large volumes are to be given, use balanced fluids such as Ringer's lactate or Plasmalyte®, as too much normal saline (NS) may lead to hyperchloremic metabolic acidosis

**Colloid Infusion** (see *Blood Products*, A15)

- includes protein colloids (albumin and gelatin solutions) and non-protein colloids (starches, e.g. hydroxyethyl starch (HES) and dextrans)
- distributes within intravascular volume
- 1:1 ratio (infusion: blood loss) only in terms of replacing intravascular volume
- HES colloids remain in intravascular space (metabolized by plasma serum amylase and renally excreted); two available in Canada: Voluven® and Pentaspan®
- beware of coagulopathy with large volume colloid infusions

**Table 7. Colloid HES Solutions**

	Concentration	Plasma Volume Expansion	Duration (h)	Maximum Daily Dose (mL/kg)
Voluven®	6%	1:1	4-6	33-50
Pentaspan®	10%	1:1.2-1.5	18-24	28

**Initial Distribution of IV Fluids**

- H<sub>2</sub>O follows ions/molecules to their respective compartments

**Colloids versus Crystalloids for Fluid Resuscitation in Critically Ill Patients**

*Cochrane DB Syst Rev 2012;6:CD000567*

**Purpose:** To evaluate the effects of colloids compared to crystalloids for fluid resuscitation, specifically when used in critically ill patients.

**Methods:** A meta-analysis was performed looking at randomized controlled trials comparing colloid vs. crystalloid use in patients requiring volume replacement. Pregnant women and neonates were excluded. Primary outcome was overall mortality.

**Results:** Results were broken down based on specific colloid. For albumin (or plasma protein fraction) the relative risk (RR) was 1.01 (95% CI 0.93-1.10) as compared to crystalloid. For hydroxyethyl starch the RR was 1.10 (95% CI 0.91-1.32). Modified gelatin had a RR of 0.91 (95% CI 0.49-1.72) and Dextran had a RR of 1.24 (95% CI 0.94-1.65). For colloids mixed in a hypertonic crystalloid as compared to isotonic crystalloid the RR was 0.88 (91% CI 0.71-1.06).

**Conclusions:** There is no evidence that use of colloids improves survival in trauma patients, burn patients or post-operative patients when compared to crystalloid solutions. Given the increased cost of colloids as compared to crystalloids, it is recommended that crystalloids be the fluid of choice in these patients.

Table 8. IV Fluid Solutions

		ECF	Ringer's Lactate	0.9% NS	0.45% NS in D5W	D5W	2/3 D5W + 1/3 NS	Plasmalyte
mEq/L	Na <sup>+</sup>	142	130	154	77	-	51	140
	K <sup>+</sup>	4	4	-	-	-	-	5
	Ca <sup>2+</sup>	4	3	-	-	-	-	-
	Mg <sup>2+</sup>	3	-	-	-	-	-	3
	Cl <sup>-</sup>	103	109	154	77	-	51	98
	HCO <sub>3</sub> <sup>-</sup>	27	28*	-	-	-	-	27
mOsm/L		280-310	273	308	154	252	269	294
pH		7.4	6.5	5.0	4.5	4.0	4.3	7.4

\*Converted from lactate

## Blood Products

- see [Hematology](#), H50

### Red Blood Cells (RBCs)

- 1U RBCs = approx. 300 mL
- 1U RBCs increases Hb by 10 g/L in a 70 kg patient
- RBCs may be diluted with colloid/crystalloid to decrease viscosity
- decision to transfuse based on initial blood volume, premonitory Hb level, present volume status, expected further blood loss, patient health status, patient consent
- massive transfusion = >1 x blood volume/24 h

### Autologous RBCs

- replacement of blood volume with one's own RBCs
- may decrease complications (infectious, febrile, etc.)
- alternative to homologous transfusion in elective procedures, but only if adequate Hb and no infection
- pre-op phlebotomy prior to elective surgery (up to 3U collected 3-5 wk before surgery)
- intraoperative salvage and filtration (cell saver); contraindicated in contaminated (e.g. bowel, abscess) or cancer cases

### Non-RBC Products

- fresh frozen plasma (FFP)
  - contains all plasma clotting factors and fibrinogen close to normal plasma levels
  - to prevent/treat bleeding due to coagulation factor depletion/deficiencies, liver impairment
- cryoprecipitate
  - contains Factors VIII and XIII, von Willebrand Factor (vWF), fibrinogen
- platelets
  - used in thrombocytopenia, massive transfusions, impaired platelet function
- albumin
  - selective intravascular volume expander
- erythropoietin
  - can be used pre-operatively to stimulate erythropoiesis

### Complications Due to Transfusion

- infectious risks: HIV, hepatitis B/C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), brucellosis, malaria, salmonellosis, measles, syphilis
- hypervolemia
- electrolyte changes: increased K<sup>+</sup> in stored blood
- dilutional coagulopathy
- dilutional thrombocytopenia
- hypothermia
- citrate toxicity
- hypocalcemia
- iron overload
- transfusion-related immunosuppression: peri-operative transfusion may be associated with increased risk of post-operative infection, increased short-term mortality and possible cancer recurrence
- see [Hematology](#), H52 for list of transfusion reactions



#### Calculating Acceptable Blood Losses (ABL)

- Blood volume
  - term infant 80 mL/kg
  - adult male 70 mL/kg
  - adult female 60 mL/kg
- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
 
$$EBV = 70 \text{ kg} \times 70 \text{ mL/kg} = 4900 \text{ mL}$$
- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion, (e.g. 70 g/L for a person with Hb(i) = 150 g/L)
 
$$Hb(f) = 70 \text{ g/L}$$
- Calculate
 
$$ABL = \frac{Hct(Hi) - Hct(Hf)}{Hct(Hi)} \times EBV$$

$$= \frac{150 - 70}{150} \times 4900$$

$$= 2613 \text{ mL}$$
- Therefore in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost.



Table 9. Immune Transfusion Reactions

Reaction	Risk	Cause	Presentation	Management
<b>Non-Hemolytic: Febrile</b>	1 in 100	<ul style="list-style-type: none"> <li>Alloantibodies to WBC, platelet, or other donor plasma antigens</li> </ul>	<ul style="list-style-type: none"> <li>Mild fever &lt;38°C with or without rigors; may be &gt;38°C with restlessness and shivering</li> <li>Nausea, facial flushing, headache, myalgias, hypotension, chest and back pain</li> <li>Occurs quickly; near completion of transfusion or within 2 h</li> </ul>	<ul style="list-style-type: none"> <li>Rule out fever due to hemolytic reaction or bacterial contamination</li> <li>Mild (&lt;38°C): decrease infusion rate and give antipyretics</li> <li>Severe: stop transfusion, give antipyretics, antihistamines and symptomatic treatment</li> </ul>
<b>Non-Hemolytic: Allergic</b>	1 in 100	<ul style="list-style-type: none"> <li>Mild allergic reaction due to IgE alloantibodies to substances in donor plasma</li> <li>Mast cells activated with histamine release</li> <li>Usually occurs in pre-exposed (e.g. multiple transfusions, multiparous)</li> </ul>	<ul style="list-style-type: none"> <li>Often have history of similar reactions</li> <li>Abrupt onset of pruritic erythema/urticaria on arms and trunk, occasionally with fever</li> <li>Less common: involvement of face, larynx and bronchioles</li> </ul>	<ul style="list-style-type: none"> <li>Mild: slow transfusion rate, IV antihistamines</li> <li>Moderate to severe: stop transfusion, IV antihistamines, subcutaneous epinephrine, hydrocortisone, IV fluids, bronchodilators</li> <li>Prophylactic: antihistamines 15-60 min prior to transfusion, washed or deglycerolized frozen RBC</li> </ul>
<b>Non-Hemolytic: Anaphylactoid</b>	<1 in 10 000	<ul style="list-style-type: none"> <li>In IgA deficient patients with anti-IgA antibodies receiving IgA-containing blood</li> <li>Immune complexes activate mast cells, basophils, eosinophils and complement system = severe symptoms after transfusion of RBC, plasma, platelets, or other components with IgA</li> </ul>	<ul style="list-style-type: none"> <li>Rare, potentially lethal</li> <li>Apprehension, urticarial eruptions, dyspnea, hypotension, laryngeal and airway edema, wheezing, chest pain, shock, sudden death</li> </ul>	<ul style="list-style-type: none"> <li>Circulatory support with fluids, catecholamines (epinephrine), bronchodilators</li> <li>Respiratory assistance as indicated</li> <li>Evaluate for IgA deficiency and anti-IgA antibodies</li> <li>Future transfusions must be free of IgA: washed/deglycerolized RBCs free of IgA, blood from IgA deficient donor</li> </ul>
<b>Transfusion Related Acute Lung Injury (TRALI)</b>	1 in 5000	<ul style="list-style-type: none"> <li>Form of noncardiogenic pulmonary edema</li> <li>Immunologic cause; not due to fluid overload or cardiac failure</li> <li>Binding of donor Ab against recipient WBC causing cytokine release leading to increased capillary permeability</li> </ul>	<ul style="list-style-type: none"> <li>Occurs 2-4 h post transfusion</li> <li>Respiratory distress: mild dyspnea to severe hypoxia</li> <li>Chest x-ray: consistent with acute pulmonary edema, but pulmonary artery and wedge pressures are not elevated</li> </ul>	<ul style="list-style-type: none"> <li>Usually resolves within 48 h with O<sub>2</sub>, mechanical ventilation, supportive treatment</li> </ul>
<b>Hemolytic: Acute (intravascular hemolysis)</b>	<1 in 40,000	<ul style="list-style-type: none"> <li>Caused by donor incompatibility with recipient's blood</li> <li>Often due to clerical error</li> <li>Antibody coated RBC is destroyed by activation of complement system</li> <li>ABO incompatibility is a common cause; other RBC Ag-Ab systems can be involved</li> </ul>	<ul style="list-style-type: none"> <li>Fever, chills, chest or back pain, hypotension, tachycardia, nausea, flushing, dyspnea, wheezing, hypoxemia, hemoglobinuria, diffuse bleeding due to DIC, acute renal failure</li> </ul>	<ul style="list-style-type: none"> <li>Stop transfusion</li> <li>Notify blood bank, confirm or rule out diagnosis – clerical check, direct Coombs, repeat grouping, Rh screen and crossmatch, serum haptoglobin</li> <li>Manage hypotension with fluids, inotropes, other blood products</li> <li>Maintain urine output with crystalloids, furosemide, dopamine, alkalize urine</li> <li>Component treatment if DIC, repeat grouping, Rh screen and crossmatch, serum haptoglobin</li> <li>Manage hypotension with fluids, inotropes, other blood products</li> <li>Component treatment (e.g. FFP, cryoprecipitate)</li> </ul>
<b>Hemolytic: Delayed (extravascular hemolysis)</b>	<1 in 7500	<ul style="list-style-type: none"> <li>Caused by donor incompatibility with recipient's blood</li> <li>Generally mild, caused by antibodies to Rh, Kell, Duffy, or Kidd antigens</li> <li>The level of antibody at the time of transfusion is too low to be detected or to cause hemolysis, later the level of antibody is increased due to secondary stimulus</li> </ul>	<ul style="list-style-type: none"> <li>Occurs in recipients sensitized to RBC antigens by previous blood transfusion or pregnancy</li> <li>Anemia, mild jaundice, fever 1-21 d post-transfusion</li> </ul>	<ul style="list-style-type: none"> <li>Supportive</li> <li>Direct Coombs, re-examination of pretransfusion specimens from the patient and donor for diagnosis</li> </ul>



## Transfusion Infection Risks

Virus	Risk per 1 unit pRBCs
HIV	1 in 8-12 million
Hepatitis C virus	1 in 5-7 million
Hepatitis B virus	1 in 1.1-1.7 million
HTLV	1 in 1-1.3 million
Syphilis	<1 in 100 million
West Nile virus	No cases since 2003

Transfusion and risk of infection in Canada: Update 2012.

*Paediatr Child Health* 2012;17:e102-e111



## A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care

*NEJM* 1999;340:409-417

**Purpose:** To determine whether a restrictive strategy of RBC transfusion and a liberal strategy produce equivalent results in critically ill patients. **Study:** Randomized controlled trial with 60 d follow-up.

**Patients:** 838 critically ill patients with euvoolemia after initial treatment who had Hb concentrations of <90 g/L within 72 h after admission to the ICU. Mean age 57.5 yr, 62.5% male.

**Intervention:** Patients were randomly assigned to either a restrictive strategy of transfusion, in which RBCs were transfused if the Hb dropped <70 g/L and Hb concentrations were maintained between 70-90 g/L, or to a liberal strategy, in which transfusions were given when the Hb dropped <100 g/L and Hb concentrations were maintained between 100-120 g/L.

**Main Outcomes:** All cause mortality rates at 30 d and 60 d, mortality rates during the stay in ICU and hospitalization, survival times during the first 30 d and rates of organ failure and dysfunction.

**Results:** Overall, 30 d mortality was similar in the two groups. However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill (8.7% vs. 16.1%) and who were less than 55 yr of age (5.7% vs. 13%), but not among patients with clinically significant cardiac disease.

The mortality rate during hospitalization was significantly lower in the restrictive strategy group (22.2% vs. 28.1%).

**Conclusions:** With the possible exception of patients with acute MI and unstable angina, a restrictive strategy of RBC transfusion is as effective as, and possibly superior to, a liberal transfusion strategy in critically ill patients.

## Extubation

- performed by trained, experienced personnel because reintubation may be required
- criteria:
  - patient must no longer have intubation requirements (see Table 3, *Tracheal Intubation*, A8)
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- laryngospasm more likely in semiconscious patient; must ensure adequate LOC
- general guidelines:
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - allow ventilation (spontaneous or controlled) with 100% O<sub>2</sub> for 3-5 min
  - suction secretions from pharynx
  - deflate cuff, remove ETT on inspiration (vocal cords abducted)
  - ensure patient is breathing adequately after extubation
  - ensure face mask for O<sub>2</sub> delivery available
  - proper positioning of patient during transfer to recovery room (e.g. lateral decubitus, head elevated)

### Complications of Extubation

- early extubation
  - aspiration
  - laryngospasm
- late extubation
  - transient vocal cord incompetence
  - edema (glottic, subglottic)
  - pharyngitis, tracheitis

### Laryngospasm

- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (e.g. by oropharyngeal secretions, blood, extubation)
- causes partial or total airway obstruction
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: bag-mask ventilation with 100% oxygen, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose succinylcholine (0.25-1 mg/kg) and reintubation if hypoxia develops

## Post-Operative Care

- pain management should be continuous from OR to post-anesthetic care unit (PACU) to hospital ward and home
- pain service may assist with management of post-operative inpatients

### Post-Operative Nausea and Vomiting (PONV)

- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), metoclopramide (Maxeran®) (not with bowel obstruction), prochlorperazine (Stemetil®), ondansetron (Zofran®), granisetron (Kytril®)

### Post-Operative Confusion and Agitation

- ABCs first – confusion or agitation can be caused by airway obstruction, hypercapnea, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers, language barriers
- metabolic disturbance (hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (stroke, raised intracranial pressure)
- drug effect (ketamine, anticholinergics)
- elderly patients are more susceptible to post-operative delirium



#### Risk Factors for Post-Operative Nausea and Vomiting (PONV)

- Young age
- Female
- History of PONV
- Non-smoker
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: N<sub>2</sub>O, opioids, volatile agents



#### Drugs for Preventing Post-Operative Nausea and Vomiting

*Cochrane DB Syst Rev* 2006;3:CD004125

**Purpose:** To evaluate the efficacy of antiemetics in preventing PONV.

**Methods:** A meta-analysis was performed looking at randomized controlled trials comparing an antiemetic to either a second antiemetic or placebo. Trials looking at dosing and/or timing of medication administration were also included. PONV was used as the primary outcome.

**Results:** 737 studies involving 103,237 patients. Eight drugs significantly reduced the occurrence of PONV, namely: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine and granisetron. Relative risk (RR) versus placebo varied between 0.60 and 0.80. Side effects included a significant increase in drowsiness for droperidol (RR 1.32) and headache for ondansetron (RR 1.16). The cumulative number needed to treat was 3.57.

**Conclusion:** Antiemetic medication is effective for reducing the occurrence of PONV. However, further investigation needs to be done to determine whether antiemetics can cause more severe (and likely rare) side effects, which could alter how liberally they are used.

# Pain Management

## Definitions

- nociception: detection, transduction and transmission of noxious stimuli
- pain: perception of nociception which occurs in the brain

## Acute Pain

- pain of short duration (<6 wk) usually associated with surgery, trauma or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

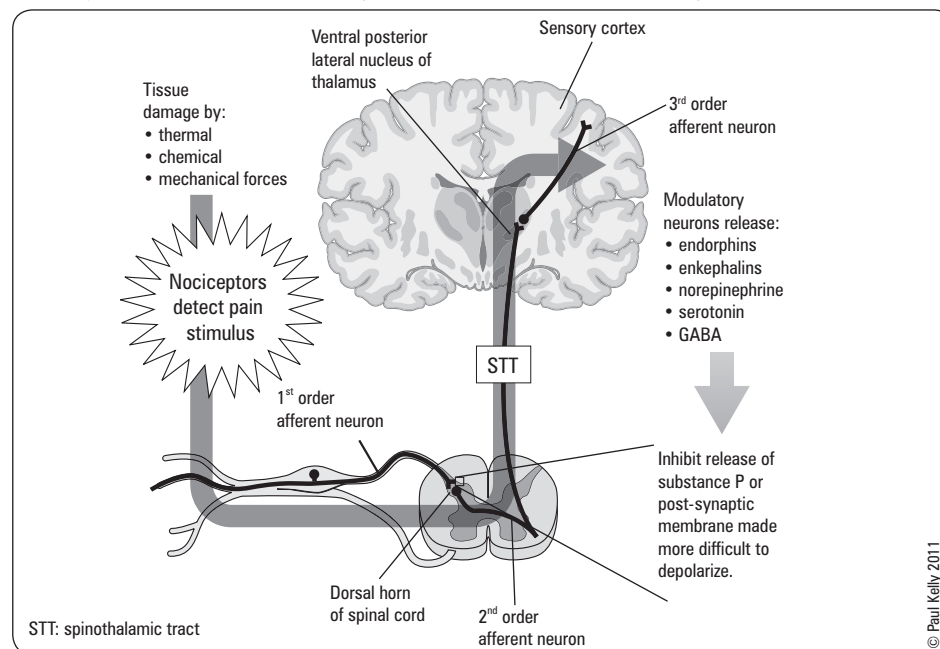


Figure 9. Acute pain mechanism

## Pharmacological Management of Acute Pain

- ask the patient to rate the pain out of 10, or use visual analog scale, to determine severity

Table 10. Commonly Used Analgesics

	Acetaminophen	NSAIDs	Opioids
<b>Examples</b>	• Tylenol®	• Aspirin®, ibuprofen, naproxen • ketorolac (IV)	• Oral: codeine, oxycodone, morphine, hydromorphone • Parenteral: morphine, hydromorphone, fentanyl
<b>Indications</b>	• First-line for mild acute pain	• Mild-moderate pain	• Oral: moderate acute pain • Parenteral: moderate-severe acute pain
<b>Mechanism of Action</b>	• Unclear, hypothesized cyclooxygenase-2 (COX-2) inhibition • Unclear, maybe modulation of endogenous cannabinoid system	• Non-selective COX-1 and 2 inhibition reducing proinflammatory prostaglandin synthesis	• Dampens nociceptive transmission between 1 <sup>st</sup> and 2 <sup>nd</sup> order neurons in the dorsal horn • Activates ascending modulatory pathways resulting in release of inhibitory neurotransmitters • Inhibits peripheral inflammatory response and hyperalgesia • Affects mood and anxiety – alleviates the affective component of perceived pain
<b>Dosing/Administration</b>	• Limited by analgesic ceiling beyond which there is no additional analgesia • Opioid-sparing • Max dose of 4 g/24 h	• Limited by analgesic ceiling beyond which there is no additional analgesia • Opioid-sparing • Significant inter-individual variation in efficacy	• No analgesic ceiling (except for codeine) • Can be administered intrathecally (spinal block) or by continuous infusion
<b>Side Effects/Toxicity</b>	• Considered relatively safe • Liver toxicity in elevated doses	• Gastric ulceration/bleeding • Decreased renal perfusion • Photosensitivity • Premature closure of the ductus arteriosus in pregnancy	• Respiratory depression • Constipation and abdominal pain • Sedation • Nausea and vomiting • Pruritus • Confusion (particularly in the elderly) • Dependence



### Opioid Equivalency

- 10 mg morphine
- 100 mg codeine
- 5 mg oxycodone
- 2 mg hydromorphone

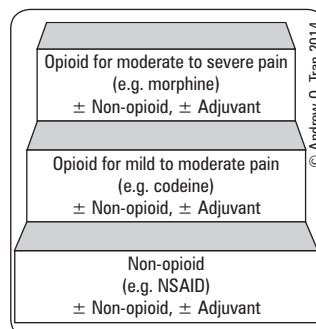


Figure 8. WHO analgesia ladder



### Use NSAIDs with Caution in Patients with:

- Asthma
- Coagulopathy
- GI ulcers
- Renal insufficiency
- Pregnancy, 3rd trimester



### Common Side Effects of Opioids

- Nausea and vomiting
- Constipation
- Sedation
- Pruritus
- Abdominal pain
- Urinary retention
- Respiratory depression

When prescribing opioids, consider:

- Breakthrough dose
- Anti-emetics
- Laxative



### PCA Parameters

- Loading dose
- Bolus dose
- Lockout interval
- Continuous infusion (optional)
- Maximum 4 h dose (limit)



### Advantages of PCA

- Improved patient satisfaction
- Fewer side effects
- Accommodates patient variability
- Accommodates changes in opioid requirements



- patient controlled analgesia (PCA)
  - involves the use of computerized pumps that can deliver a constant infusion as well as bolus breakthrough doses of parenterally-administered opioid analgesics
  - limited by lockout intervals
  - most commonly used agents: morphine and hydromorphone
  - refer to Table 14, A26 for suggested infusion rate, PCA dose and lockout intervals

### Opioid Antagonists (naloxone, naltrexone)

- opioid overdose manifests primarily at CNS (e.g. respiratory depression) – manage ABCs
- opioid antagonists competitively inhibit opioid receptors, predominantly  $\mu$  receptors
- naloxone is short-acting ( $t_{1/2} = 1$  h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
- naltrexone is longer-acting ( $t_{1/2} = 10$  h); less likely to see return of opioid effects
- relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, hypertension, re-emergence of pain, pulmonary edema, seizures (essentially opioid withdrawal)

### Neuropathic Pain

- pain caused by peripheral or central nervous system injury, often described as burning, lancinating, shooting, or tingling
- results in allodynia (pain in response to normally painless stimuli) or hyperalgesia (increased sensitivity to painful stimuli)
- consider adding anticonvulsants (gabapentin, pregabalin) or low-dose tricyclic antidepressant as opioids are ineffective

### Chronic Pain

- pain of duration or intensity that persists beyond normal tissue healing and adversely affects functioning
- may have nociceptive and neuropathic components; dysregulation of analgesic pathways implicated
- in the peri-operative period, consider continuing regular long-acting analgesics, and augmenting with regional techniques, adjuvants, additional opioid analgesia, and non-pharmacological techniques



#### Patient Controlled Opioid Analgesia versus Conventional Opioid Analgesia for Postoperative Pain

Cochrane DB Syst Rev 2006;4:CD003348

**Purpose:** To evaluate the efficacy of patient controlled analgesia (PCA) as compared to conventional 'as-needed' analgesia administration providing pain relief in post-operative patients.

**Methods:** Meta-analyses of randomized controlled trials comparing PCA vs. conventional administration of opioid analgesia. Assessment employed a visual analog scale (VAS) for pain intensity along with overall analgesic consumption, patient satisfaction, length of stay and adverse side effects.

**Results:** 55 studies with a total of 2023 patients receiving PCA and 1838 patients with standard as-needed opioid administration. PCA provided significantly better pain control through 72 h post-operatively, but patients consumed significantly more opioids ( $> 7$  mg morphine/24 h,  $P < 0.05$ ). Significantly more patients reported pruritus in the PCA group compared to control with a number needed to harm of 13. No significant difference in overall length of stay in hospital, sedation level, nausea/vomiting or urinary retention.

**Conclusions:** PCA is more effective than standard as-needed administration for reducing post-operative pain. However, patients using PCA consume more opioids overall and have more pruritus.

## Regional Anesthesia

### Definition of Regional Anesthesia

- local anesthetic agent (LA) applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) for the purpose of reducing or preventing impulse transmission
- no CNS depression (unless overdose of local anesthetic); patient remains conscious
- regional anesthetic techniques categorized as follows:
  - epidural and spinal anesthesia (neuraxial anesthesia)
  - peripheral nerve blocks
  - IV regional anesthesia (e.g. Bier block)

### Preparation for Regional Anesthesia

#### Patient Preparation

- thorough pre-operative evaluation and assessment of patient
- technique explained to patient
- sedation may be indicated before block
- monitoring should be as extensive as for general anesthesia

#### Relative Indications for Regional Anesthesia

- avoids some of the dangers of general anesthesia (e.g. known difficult intubation, severe respiratory failure, etc.)
- patient specifically requests regional anesthesia
- high quality post-operative pain relief
- general anesthesia not available/contraindicated
- titration of LA dosage for differential blockade (e.g. can block pain but preserve motor function)

#### Complications of Regional Anesthesia

- failure of technique/inadequate anesthesia
- unintentional total spinal anesthesia
- systemic drug toxicity due to overdose or intravascular injection (leading to CNS and CVS complications)
- injury to nerve root/spinal cord (nerve deficit), to epidural vein (hematoma), to peripheral nerve (intraneural injection)
- infection (e.g. osteitis, epidural abscess, meningitis)
- spinal and epidural: sympathetic blockade causing hypotension and bradycardia (occurs early, followed by sensory then motor blockade)
- post-dural puncture headache



#### Benefits of Regional Anesthesia

- Reduced peri-op pulmonary complications
- Reduced peri-op analgesia requirements
- Decreased PONV
- Reduced peri-op blood loss
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE



## Epidural and Spinal Anesthesia

### Anatomy of Spinal/Epidural Area

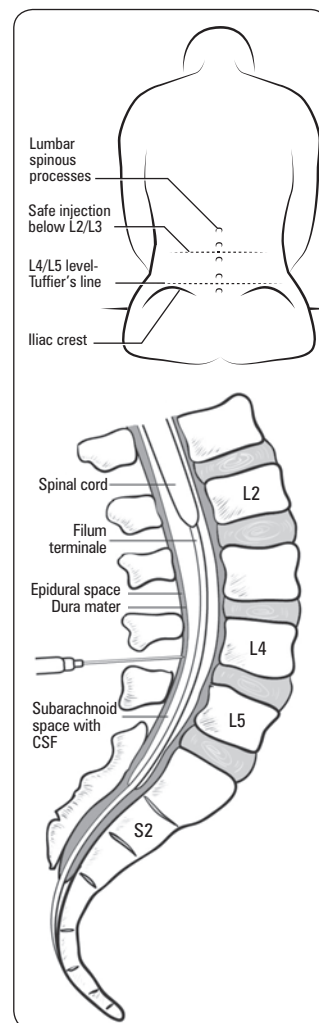
- spinal cord extends to L2, dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

**Table 11. Epidural versus Spinal Anesthesia**

	Epidural	Spinal
<b>Deposition Site</b>	LA injected in epidural space (space between ligamentum flavum and dura) Initial blockade is at the spinal roots followed by some degree of spinal cord anesthesia as LA diffuses into the subarachnoid space through the dura	LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots
<b>Onset</b>	Significant blockade requires 10-15 min Slower onset of side effects	Rapid blockade (onset in 2-5 min)
<b>Effectiveness</b>	Effectiveness of blockade can be variable	Very effective blockade
<b>Difficulty</b>	Technically more difficult; greater failure rate	Easier to perform due to visual confirmation of CSF flow
<b>Patient Positioning</b>	Position of patient not as important; specific gravity not an issue	Hyperbaric LA solution – position of patient important
<b>Specific Gravity/Spread</b>	Solutions injected here spread throughout the potential space; specific gravity of solution does not affect spread	LA solution may be made hyperbaric (of greater specific gravity than the cerebrospinal fluid by mixing with 10% dextrose, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space)
<b>Dosage</b>	Larger volume/dose of LA (usually > toxic IV dose)	Smaller dose of LA required (usually < toxic IV dose)
<b>Continuous Infusion</b>	Use of catheter allows for continuous infusion or repeat injections	None
<b>Complications</b>	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), i.e. "high spinal" Epidural or subarachnoid hematoma Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications) Systemic toxicity of LA (accidental intravenous) Catheter complications (shearing, kinking, vascular or subarachnoid placement) Infection Dural puncture	Failure of technique Hypotension Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), i.e. "high spinal" Epidural or subarachnoid hematoma Post-spinal headache (CSF leak) Transient paresthesias Spinal cord trauma, infection
<b>Combined Spinal-Epidural</b>	Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter	

### Contraindications to Spinal/Epidural Anesthesia

- absolute contraindications
  - lack of proper equipment or trained personnel
  - lack of IV access
  - allergy to LA
  - infection at puncture site or underlying tissues
  - coagulopathies/anti-coagulation
  - raised ICP
  - sepsis/bacteremia
  - hemodynamic instability/uncorrected hypovolemia



**Figure 10. Landmarks for placement of epidural/spinal**



#### Landmarking Epidural/Spinal Anesthesia

Spinous processes should be maximally flexed

L4 spinous processes found between iliac crests

Common sites of insertion are L3-L4 and L4-L5



#### Classic Presentation of Dural Puncture Headache

- Onset 6 h-3 d after dural puncture
- Postural component (worse sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia

- relative contraindications
  - pre-existing neurological disease
  - aortic/mitral valve stenosis (i.e. fixed cardiac output states)
  - previous spinal surgery, severe kyphoscoliosis
  - severe/unstable psychiatric disease or emotional instability

## Peripheral Nerve Blocks

- utilizes ultrasound guidance and electrical stimulation (needle will stimulate target nerve/plexus), may be used to guide deposition of local anesthetic around nerve while avoiding neural trauma or intraneural injection
- approximately 2-4 per 10,000 risk of late neurologic injury
- most major nerves or nerve plexi can be targeted (e.g. brachial plexus block, femoral nerve block, sciatic nerve block, etc.)

### Contraindications to Peripheral Nerve Blockade

- allergy to LA
- patient refusal, lack of cooperation
- lack of resuscitation equipment
- lack of IV access
- certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
- local infection at block site
- bleeding disorder

## Local Anesthesia

### Local Anesthetic Agents (LA)

- see Table 19 for list of LA agents, A28

#### Definition and Mode of Action

- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptors on the cytosolic side of the  $\text{Na}^+$  channel, inhibiting  $\text{Na}^+$  flux and thus blocking impulse conduction
- different types of nerve fibres undergo blockade at different rates

#### Absorption, Distribution, Metabolism

- LA readily crosses the blood-brain barrier (BBB) once absorbed into the bloodstream
- ester-type LA (procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- amide-type LA (lidocaine, bupivacaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

#### Selection of LA

- choice of LA depends on
  - onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA and the faster the onset of action)
  - duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  - potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  - unique needs (e.g. sensory blockade with relative preservation of motor function by bupivacaine at low doses)
  - potential for toxicity

#### Systemic Toxicity

- see Table 19, A28 for maximum doses, potency and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption
- CNS effects first appear to be excitatory due to initial block of inhibitory fibres; then subsequent block of excitatory fibres
- CNS effects (in order of appearance)
  - numbness of tongue, perioral tingling, metallic taste
  - disorientation, drowsiness
  - tinnitus



**Reduction of Postoperative Mortality and Morbidity with Epidural or Spinal Anaesthesia: Results from Overview of Randomized Trials**  
*BMJ* 2000;321:1-12

**Purpose:** To obtain reliable estimates of the effects of neuraxial blockade with epidural or spinal anesthesia on postoperative morbidity and mortality after various surgeries with or without general anesthesia.

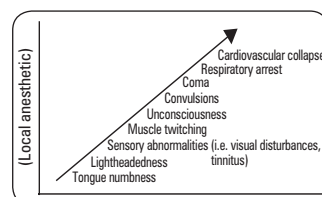
**Study:** Systematic review of all trials with randomization to intra-operative neuraxial blockade versus not.

**Patients:** 141 trials including 9559 patients.

**Main Outcomes:** All cause mortality, MI, PE, DVT, transfusion requirements, pneumonia, other infections, respiratory depression and renal failure.

**Results:** With neuraxial blockade, overall mortality was reduced by about one third. Neuraxial blockade reduced the risk of PE by 55%, DVT by 44%, transfusion requirements by 50%, pneumonia by 39% and respiratory depression by 59%. There were also reductions in MI and renal failure. These mortality reductions are irrespective of surgical group, type of blockade (epidural or spinal) or whether neuraxial blocker was combined with general anesthetic.

**Conclusions:** Neuraxial blockade reduces postoperative mortality and other serious complications.



**Figure 11. Local anesthetic systemic toxicity**

- visual disturbances
- muscle twitching, tremors
- unconsciousness
- convulsions, seizures
- generalized CNS depression, coma, respiratory arrest
- CVS effects
  - vasodilation, hypotension
  - decreased myocardial contractility
  - dose-dependent delay in cardiac impulse transmission
    - ♦ prolonged PR, QRS intervals
    - ♦ sinus bradycardia
  - CVS collapse
- treatment of systemic toxicity
  - early recognition of signs, get help
  - 100% O<sub>2</sub>, manage ABCs
  - diazepam or sodium thiopental may be used to increase seizure threshold
  - manage arrhythmias (see ACLS Guidelines, A28)
  - Intralipid® 20% to bind local anesthetic in circulation

## Local Infiltration and Hematoma Blocks

### Local Infiltration

- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerve endings
- suitable for small incisions, suturing, excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100,000-1:200,000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

### Fracture Hematoma Block

- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

## Topical Anesthetics

- various preparations of local anesthetics available for topical use, may be a mixture of agents, e.g. EMLA cream is a combination of 2.5% lidocaine and prilocaine
- must be able to penetrate the skin or mucous membrane

## Obstetrical Anesthesia

### Physiologic Changes in Pregnancy

- airway
  - possible difficult airway as tissues become edematous and friable especially in labour
- respiratory
  - decreased FRC and increased O<sub>2</sub> consumption → desaturation occurs more quickly during apnea
- cardiovascular system
  - increased blood volume > increased RBC mass → mild anemia
  - decreased SVR proportionately greater than increased CO → decreased BP
  - prone to decreased BP due to aortocaval compression – therefore for surgery, a pregnant patient is positioned in left uterine displacement using a wedge under her right flank
- central nervous system
  - decreased MAC due to hormonal effects
  - increased block height due to engorged epidural veins
- gastrointestinal system
  - delayed gastric emptying
  - increased volume and acidity of gastric fluid
  - decreased LES tone
  - increased abdominal pressure
  - combined, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity



**Where Not to Use LA with Epinephrine**  
“Ears, Fingers, Toes, Penis, Nose”



**The Effect of Epidural Analgesia on Labour, Maternal, and Neonatal Outcomes: A Systematic Review**

*Am J Obstet Gynecol* 2002;186:S69-77

**Study:** Meta-analysis of 14 studies with 4324 women.

**Selection Criteria:** RCTs and prospective cohort studies between 1980-2001 comparing epidural analgesia to parenteral opioid administration during labour.

**Types of Participants:** Healthy women with uneventful pregnancies.

**Intervention:** Participants were randomized to either epidural analgesia or parenteral opioid administration during labour.

**Outcomes and Results:** Maternal – there were no differences between the 2 groups in first-stage labour length, incidence of Caesarean delivery, incidence of instrumented vaginal delivery for dystocia, nausea, or mid-to-low back pain post-partum. However, second-stage labour length was longer (mean = 15 min) and there were greater reports of fever and hypotension in the epidural group. Also, lower pain scores and greater satisfaction with analgesia were reported among the epidural group. There was no difference in lactation success at 6 wk and urinary incontinence was more frequent in the epidural group immediately post-partum, but not at 3 mo or 1 yr (evidence from PC studies only).

**Neonatal** – there were no differences between the 2 groups for incidence of fetal heart rate abnormalities, intrapartum meconium, poor 5-min Apgar score, or low umbilical artery pH. However, the incidence of poor 1-min Apgar scores and need for neonatal naloxone were higher in the parenteral opioid group.

**Conclusions:** Epidural analgesia is a safe intrapartum method for labour pain relief and women should not avoid epidural analgesia for fear of neonatal harm, Caesarean delivery, breastfeeding difficulties, long-term back pain or long-term urinary incontinence.

### Options for Analgesia during Labour

- psychoprophylaxis – Lamaze method
  - patterns of breathing and focused attention on fixed object
- systemic medication
  - easy to administer, but risk of maternal or neonatal depression
  - opioids most commonly used if delivery is not expected within 4 h
- inhalational analgesia
  - easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
  - 50% nitrous oxide
- neuraxial anesthesia
  - provides excellent analgesia with minimal depressant effects
  - hypotension is the most common complication
  - maternal BP monitored q2-5 min for 15-20 min after initiation and regularly thereafter
  - epidural usually given as it preferentially blocks sensation, leaving motor function intact

### Options for Caesarean Section

- neuraxial: spinal or epidural
- general: used if contraindications or time precludes regional blockade

## Pediatric Anesthesia

### Respiratory System

- in comparison to adults, anatomical differences in infants include
  - large head, short trachea/neck, large tongue, adenoids and tonsils
  - narrow nasal passages (obligate nasal breathers until 5 mo)
  - narrowest part of airway at the level of the cricoid vs. glottis in adults
  - epiglottis is longer, U shaped and angled at 45 degrees; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include
  - faster RR, immature respiratory centres which are depressed by hypoxia/hypercapnea (airway closure occurs in the neonate at the end of expiration)
  - less oxygen reserve during apnea – decreased total lung volume, vital and functional reserve capacity together with higher metabolic needs
  - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm and higher resistance to airflow

### Cardiovascular System

- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume lost
- children have a high HR and low BP
- CO is dependent on HR, not stroke volume because of low heart wall compliance; therefore, bradycardia → severe compromise in CO

### Temperature Regulation

- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant's head, humidification of inspired gases and warming of infused solutions

### Central Nervous System

- MAC of halothane is increased compared to the adult (i.e. 0.75% adult, 0.87% neonates, 1.2% infant)
- NMJ is immature for the first 4 wk of life and thus there is an increased sensitivity to non-depolarizing relaxants
- parasympathetics mature at birth, sympathetics mature at 4-6 mo → autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

### Glucose Maintenance

- infants less than 1 yr old can become seriously hypoglycemic during pre-operative fasting and post-operatively if feeding is not recommenced as soon as possible
- after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

### Pharmacology

- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB



### Nociceptive Pathways in Labour and Delivery

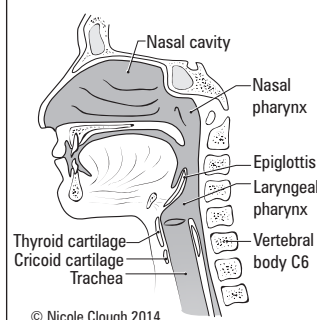
#### Labour

- Cervical dilation and effacement stimulates visceral nerve fibres entering the spinal cord at T10-L1

#### Delivery

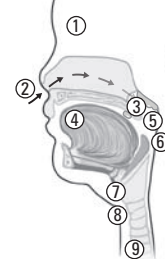
- Distention of lower vagina and perineum causes somatic nociceptive impulses via the pudendal nerve entering the spinal cord at S2-S4

### Adult Upper Airway



© Nicole Clough 2014

### Child Upper Airway



1. Large head
2. Newborns are obligate nasal breathers
3. Adenoid and tonsils
4. Larger tongue in proportion to mouth
5. Smaller pharynx
6. Larger and more flaccid epiglottis
7. Larynx is more superior and anterior
8. Narrowest point at cricoid cartilage
9. Trachea is more narrow and less rigid

© Andrew Q. Tran 2014 (after Leanne Chan 2011)

**Figure 12. Comparison of pediatric vs. adult airway**



To increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume.

**Neonate:** 30-40 breaths/min

**Age 1-13:**  $(24 - [\text{age}/2])$  breaths/min



### ETT Sizing in Pediatrics

Diameter (mm) of tracheal tube in children after 1 year =  $(\text{age}/4) + 4$

Length (cm) of tracheal tube =  $(\text{age}/2) + 12$

- muscle relaxants
  - non-depolarizing
    - ♦ immature NMJ, variable response
  - depolarizing
    - ♦ must pre-treat with atropine or may experience profound bradycardia and/or sinus node arrest due to PNS > SNS (also dries oral secretions)
    - ♦ more susceptible to arrhythmias, hyperkalemia, rhabdomyolysis, myoglobinemia, masseter spasm and malignant hyperthermia

## Uncommon Complications

### Malignant Hyperthermia (MH)

- hypermetabolic disorder of skeletal muscle
- due to an uncontrolled increase in intracellular  $\text{Ca}^{2+}$  (because of an anomaly of the ryanodine receptor which regulates the  $\text{Ca}^{2+}$  channel in the sarcoplasmic reticulum of skeletal muscle)
- autosomal dominant inheritance
- incidence of 1-5 in 100,000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH include
  - all inhalational agents except nitrous oxide
  - depolarizing muscle relaxants: SCh

#### Clinical Picture

- onset: immediate or hours after contact with trigger agent
  - increased oxygen consumption
  - increased  $\text{ET}_{\text{CO}_2}$  on capnograph
  - tachycardia/dysrhythmia
  - tachypnea/cyanosis
  - diaphoresis
  - hypertension
  - increased temperature (late sign)
- muscular symptoms
  - trismus (masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  - tender, swollen muscles due to rhabdomyolysis
  - trunk or total body rigidity

#### Complications

- coma
- DIC
- rhabdomyolysis
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema
- can be fatal if untreated

#### Prevention

- suspect MH in patients with a family history of problems/death with anesthetic
- avoid all trigger medications (use regional if possible) and use vapour free equipment
- central body temp and  $\text{ET}_{\text{CO}_2}$  monitoring

#### Malignant Hyperthermia Management [Based on Malignant Hyperthermia Association of the U.S. (MHAUS) Guidelines, 2008]

1. notify surgeon, discontinue volatile agents and succinylcholine, hyperventilate with 100% oxygen at flows of 10 L/min or more; halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
  - repeat until there is control of signs of MH; sometimes up to 30 mg/kg is necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis
4. cool patients with core temperature  $>39^\circ\text{C}$ 
  - lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
  - stop cooling if temperature is  $<38^\circ\text{C}$  to prevent drift to  $<36^\circ\text{C}$
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
  - use standard drug therapy except  $\text{Ca}^{2+}$  channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene



#### Signs of Malignant Hyperthermia

- Unexplained rise in  $\text{ET}_{\text{CO}_2}$
- Increase in minute ventilation
- Tachycardia
- Rigidity
- Hyperthermia (late sign)



#### Basic Principles of MH Management

##### "Some Hot Dude Better Get Iced Fluids Fast"

Stop all triggering agents, give 100%  $\text{O}_2$   
 Hyperventilate  
 Dantrolene 2.5 mg/kg every 5 min  
 Bicarbonate  
 Glucose and insulin  
 IV Fluids; cool patient to  $38^\circ\text{C}$   
 Fluid Output; consider furosemide  
 Tachycardia: be prepared to treat VT



6. hyperkalemia
  - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
  - bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg for life-threatening hyperkalemia and check glucose levels hourly
7. follow  $ET_{CO_2}$ , electrolytes, blood gases, creatine kinase (CK), core temperature, urine output/colour with Foley catheter, coagulation studies
  - if CK and/or potassium rises persistently or urine output falls to  $<0.5$  mL/kg/h, induce diuresis to  $>1$  mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids and propofol
9. transfer to ICU bed

## Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- 1 in 50 people will be heterozygous for an abnormal pseudocholinesterase allele
- heterozygotes will experience a prolonged duration of muscular blockade (2-3x normal)
- homozygotes will have a greatly increased duration of blockade (4-8 h) following administration of SCh
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors)

## Common Medications

Table 12. Intravenous Induction Agents

	Propofol (Diprivan®)	Thiopental (sodium thiopental, sodium thiopentone)	Ketamine (Ketalar®, Ketaject®)	Benzodiazepines [midazolam (Versed®), diazepam (Valium®), lorazepam (Ativan®)]
<b>Class</b>	• Alkylphenol – hypnotic	• Ultra-short acting thiobarbiturate – hypnotic	• Phencyclidine (PCP) derivative – dissociative	• Benzodiazepines – anxiolytic
<b>Action</b>	• Inhibitory at GABA synapse • Decreased cerebral metabolic rate and blood flow, decreased ICP, decreased SVR, decreased BP and decreased SV	• Decreased time $Cl^-$ channels open, facilitating GABA and suppressing glutamic acid • Decreased cerebral metabolism and blood flow, decreased CPP, decreased $CO_2$ , decreased BP, decreased reflex tachycardia, decreased respiration	• May act on NMDA, opiate and other receptors • Increased HR, increased BP, increased SVR, increased coronary flow, increased myocardial $O_2$ uptake, CNS and respiratory depression, bronchial smooth muscle relaxation	• Causes increased glycine inhibitory neurotransmitter, facilitates GABA • Produces antianxiety and skeletal muscle relaxant effects • Minimal cardiac depression
<b>Indications</b>	• Induction • Maintenance • Total intravenous anesthesia (TIVA)	• Induction • Control of convulsive states	• Major trauma, hypovolemia, severe asthma because sympathomimetic	• Used for sedation, amnesia and anxiolysis
<b>Caution</b>	• Allergy (egg, soy) • Pts who cannot tolerate sudden decreased BP (i.e. fixed cardiac output or shock)	• Allergy to barbiturates • Uncontrolled hypotension, shock, cardiac failure • Porphyria, liver disease, status asthmaticus, myxedema	• Ketamine allergy • TCA medication (interaction causes HTN and dysrhythmias) • History of psychosis • Pts who cannot tolerate HTN (e.g. CHF, increased ICP, aneurysm)	• Marked respiratory depression
<b>Dosing</b>	• IV induction: 2.5-3.0 mg/kg (less with opioids) • Unconscious $<1$ min • Lasts 4-6 min • $t_{1/2}=55$ min • Decreased post-op sedation, recovery time, N/V	• IV induction: 3-5 mg/kg • Unconscious about 30 s • Lasts 5 min • Accumulation with repeat dosing – not for maintenance • $t_{1/2} = 5-10$ h • Post-op sedation lasts hours	• IV induction 1-2 mg/kg • Dissociation in 15 s, analgesia, amnesia and unconsciousness in 45-60 s • Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 h • $t_{1/2} = \sim 3$ h	• Onset less than 5 min if given IV • Duration of action long but variable/somewhat unpredictable
<b>Special Considerations</b>	• 0-30% decreased BP due to vasodilation • Reduce burning at IV site by mixing with lidocaine	• Combining with rocuronium causes precipitates to form	• High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions) • Pretreat with glycopyrrolate to decrease salivation	• Antagonist: flumazenil (Anexate®) competitive inhibitor, 0.2 mg IV over 15 s, repeat with 0.1 mg/min (max of 2 mg), $t_{1/2}$ of 60 min • Midazolam also has amnestic (antegrade) effect and decreased risk of thrombophlebitis



Table 13. Opioids

Agent	Relative Dose to 10 mg Morphine IV	Moderate Dose	Onset	Duration	Special Considerations
Codeine	200 mg PO	15-30 mg PO	Late (30-60 min)	Moderate (4-6 h)	Primarily post-operative use, not for IV use
Meperidine (Demerol®)	75 mg IV	2-3 mg/kg IV	Moderate (10 min)	Moderate (2-4 h)	Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures
Morphine	10 mg IV 20 mg PO	0.2-0.3 mg/kg IV 0.4-0.6 mg/kg PO	Moderate (5-10 min)	Moderate (4-5 h)	Histamine release leading to decrease in BP
Oxycodone controlled release (Oxyneo®)	15 mg PO	10-20 mg PO (no IV)	Late (30-45 min)	Long (8-12 h)	Do not split, crush or chew tablet
Oxycodone regular tablet (Oxy IR®)	15 mg PO (no IV)	5-15 mg PO	Moderate (15 min)	Moderate (3-6 h)	Percocet® = oxycodone 5 mg + acetaminophen 325 mg
Hydromorphone (Dilaudid®)	2 mg IV 10 mg PO	40-60 µg/kg IV 2-4 mg PO	Moderate (15 min)	Moderate (4-5 h)	
Fentanyl	100 µg IV	2-3 µg/kg IV	Rapid (<5 min)	Short (0.5-1 h)	Transient muscle rigidity in very high doses
Remifentanyl	100 µg IV	0.5-1.5 µg/kg IV	Rapid (1-3 min)	Ultra short (<10 min)	Only use during induction and maintenance of anesthesia

In general, parenteral route is 2-3 times more potent than oral

Table 14. Opioid PCA Doses

Agent	PCA Dose	PCA Lockout Interval	PCA 4 h Maximum
Morphine	1 mg	5 min	30 mg
Fentanyl	25-50 µg	5 min	400 µg
Hydromorphone	0.2 mg	5 min	6 mg

Table 15. Volatile Inhalational Agents

	Sevoflurane	Desflurane	Isoflurane	Enflurane	Halothane	Nitrous oxide (N <sub>2</sub> O)*
MAC (% gas in O <sub>2</sub> )	2.0	6.0	1.2	1.7	0.8	104
CNS	Increased ICP	Increased ICP	Decreased cerebral metabolic rate Increased ICP	ECG seizure-like activity Increased ICP	Increased ICP and cerebral blood flow	—
Resp	Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory CO <sub>2</sub> reflexes, bronchodilation					—
CVS	Less decrease of contractility, stable HR	Tachycardia with rapid increase in concentration	Decreased BP and CO, increased HR, theoretical chance of coronary steal**	Stable HR, decreased contractility	Decreased BP, CO, HR and conduction Sensitizes myocardium to epinephrine-induced arrhythmias	Can cause decreased HR in pediatric cases in those with existing heart disease
MSK	Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation					

\*Properties and Adverse Effects of N<sub>2</sub>O

Due to its high MAC, nitrous oxide is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only  
Second Gas Effect: see *Determinants of Speed of Onset of Volatile Anesthetics* sidebar, A6

Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen and ETT cuff will markedly enlarge if N<sub>2</sub>O is administered  
Diffusion hypoxia: during anesthesia, the washout of N<sub>2</sub>O from body stores into alveoli can dilute the alveolar [O<sub>2</sub>], creating a hypoxic mixture if the original [O<sub>2</sub>] is low

\*\*Coronary steal: isoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion (e.g. stents, atherosclerosis)

**Table 16. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)**

<b>Mechanism of Action</b>	Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh
<b>Intubating Dose</b>	1-1.5 mg/kg
<b>Onset</b>	30-60 s – RAPID (fastest of all muscle relaxants)
<b>Duration</b>	3-5 min – SHORT (no reversing agent for SCh)
<b>Metabolism</b>	SCh is hydrolyzed by plasma cholinesterase (pseudocholinesterase), found only in plasma and not at the NMJ
<b>Indications</b>	<ul style="list-style-type: none"> <li>• Assist intubation</li> <li>• Increased risk of aspiration (need rapid paralysis and airway control)</li> <li>• Short procedures (e.g. full stomach), hiatus hernia, obesity, pregnancy, trauma</li> <li>• Electroconvulsive therapy (ECT)</li> <li>• Laryngospasm</li> </ul>
<b>Side Effects</b>	<ol style="list-style-type: none"> <li>1. SCh also stimulates muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors) <ul style="list-style-type: none"> <li>• May cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children)</li> </ul> </li> <li>2. Hyperkalemia <ul style="list-style-type: none"> <li>• Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors</li> <li>• Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells</li> <li>• Patients at risk: <ul style="list-style-type: none"> <li>▪ 3rd degree burns 24 h-6 mo after injury</li> <li>▪ Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy)</li> <li>▪ Severe intra-abdominal infections</li> <li>▪ Severe closed head injury</li> <li>▪ Upper motor neuron lesions</li> </ul> </li> </ul> </li> <li>3. Can trigger MH</li> <li>4. Increased ICP/intraocular pressure/intragastric pressure (no increased risk of aspiration if competent lower esophageal sphincter)</li> <li>5. Fasciculations, post-op myalgia – may be minimized if small dose of non-depolarizing agent given before SCh administration</li> </ol>
<b>Contraindications</b>	
<b>Absolute</b>	Known hypersensitivity or allergy, positive history of malignant hyperthermia, myotonia (m. congenita, m. dystrophica, paramyotonia congenita), high risk for hyperkalemic response
<b>Relative</b>	Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury

**Table 17. Non-Depolarizing Muscle Relaxants (Competitive)**

<b>Mechanism of Action</b>	Competitive blockade of postsynaptic ACh receptors preventing depolarization				
<b>Classification</b>	<b>Short</b>	<b>Intermediate</b>			<b>Long</b>
	Mivacurium	Rocuronium	Vecuronium	Cisatracurium	Pancuronium
<b>Intubating Dose (mg/kg)</b>	0.2	0.6-1.0	0.1	0.2	0.1
<b>Onset (min)</b>	2-3	1.5	2-3	3	3-5
<b>Duration (min)</b>	15-25	30-45	45-60	40-60	90-120
<b>Metabolism</b>	Plasma cholinesterase	Liver (major) Renal (minor)	Liver	Hofmann Eliminations	Renal (major) Liver (minor)
<b>Indications</b>	Assist intubation, assist mechanical ventilation in some ICU patients, reduce fasciculations and post-op myalgias secondary to SCh				
<b>Side Effects:</b>					
<b>Histamine Release</b>	Yes	No	No	No	No
<b>Other</b>	—	—	—	—	Tachycardia
<b>Considerations</b>	Increased duration of action in renal or liver failure	Quick onset of rocuronium allows its use in rapid sequence induction Cisatracurium is good for patients with renal or hepatic insufficiency			Pancuronium if increased HR and BP desired

**Table 18. Reversal Agents for Non-Depolarizing Relaxants**

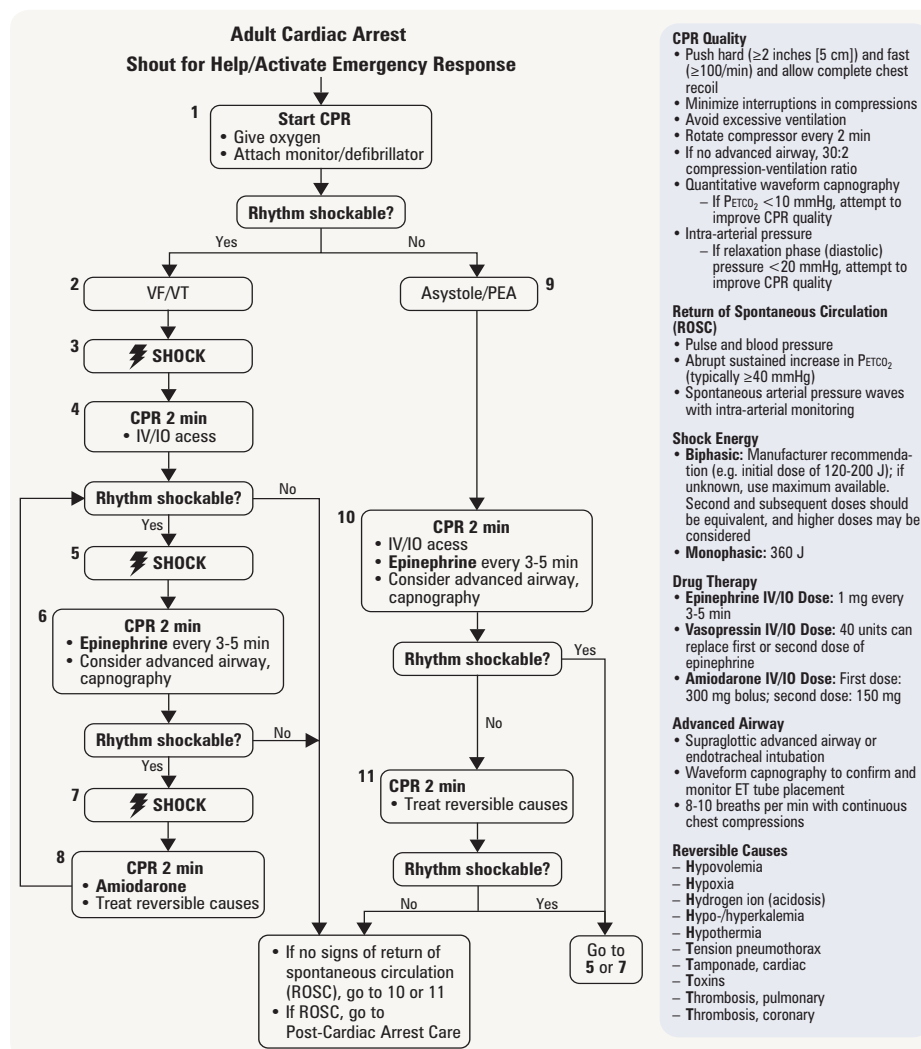
Cholinesterase Inhibitor	Neostigmine	Pyridostigmine	Edrophonium
Onset and Duration	Intermediate	Longest	Shortest
Mechanism of Action	Inhibits enzymatic degradation of ACh, increases ACh at nicotinic and muscarinic receptors, displaces non-depolarizing muscle relaxants Muscarinic effects of reversing agents include unwanted bradycardia, salivation and increased bowel peristalsis*		
Dose	0.04-0.08 mg/kg	0.1-0.4 mg/kg	0.5-1 mg/kg
Recommended Anticholinergic	Glycopyrrolate	Glycopyrrolate	Atropine
Dose of Anticholinergic per mg	0.2 mg	0.05 mg	0.014 mg

\*Atropine and glycopyrrolate are anticholinergic agents administered during the administration of reversal agents to minimize muscarinic effects

**Table 19. Local Anesthetic Agents**

	Maximum Dose	Maximum Dose with Epinephrine	Potency	Duration
chlorprocaine	11 mg/kg	14 mg/kg	Low	15-30 min
lidocaine	5 mg/kg	7 mg/kg	Medium	1-2 h
bupivacaine	2.5 mg/kg	3 mg/kg	High	3-8 h
ropivacaine	2.5 mg/kg	3 mg/kg	High	2-8 h

## Advanced Cardiac Life Support (ACLS) Guidelines

**Figure 13. Adult cardiac arrest algorithm**

Reprinted with permission: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Adult Advanced Cardiovascular Life Support. Circulation 2010;122[suppl 3]:S729-S767 ©2010 American Heart Association, Inc.

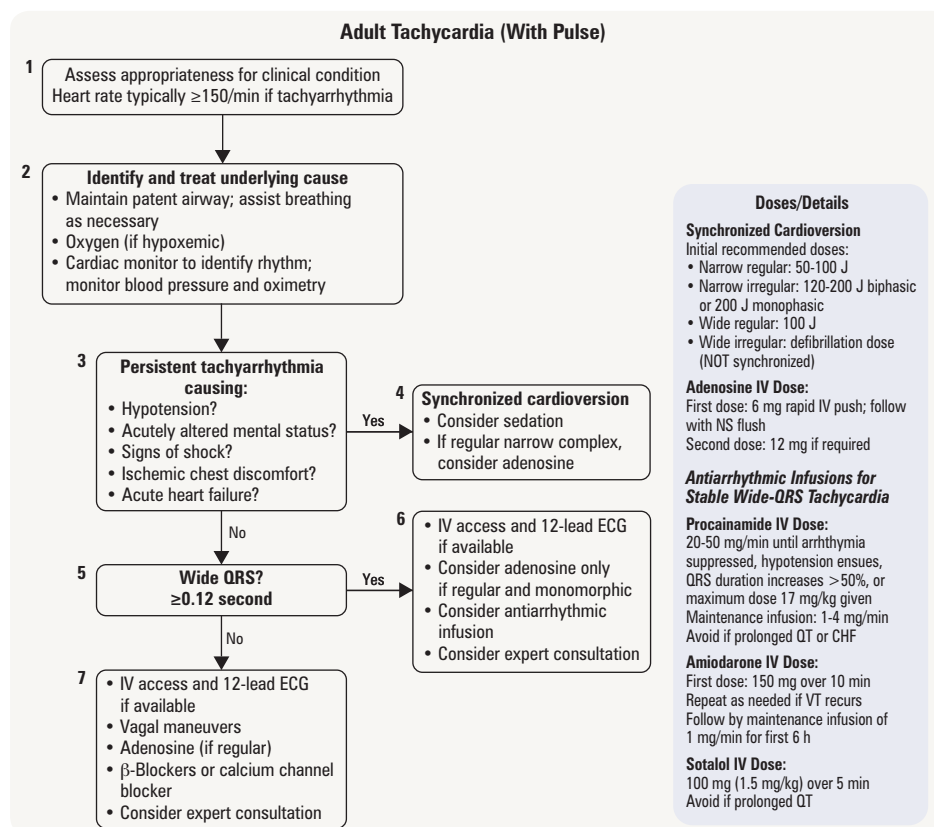


Figure 14. Adult tachycardia algorithm

Reprinted with permission: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Adult Advanced Cardiovascular Life Support. Circulation 2010;122[suppl 3]:S729-S767 ©2010 American Heart Association, Inc.

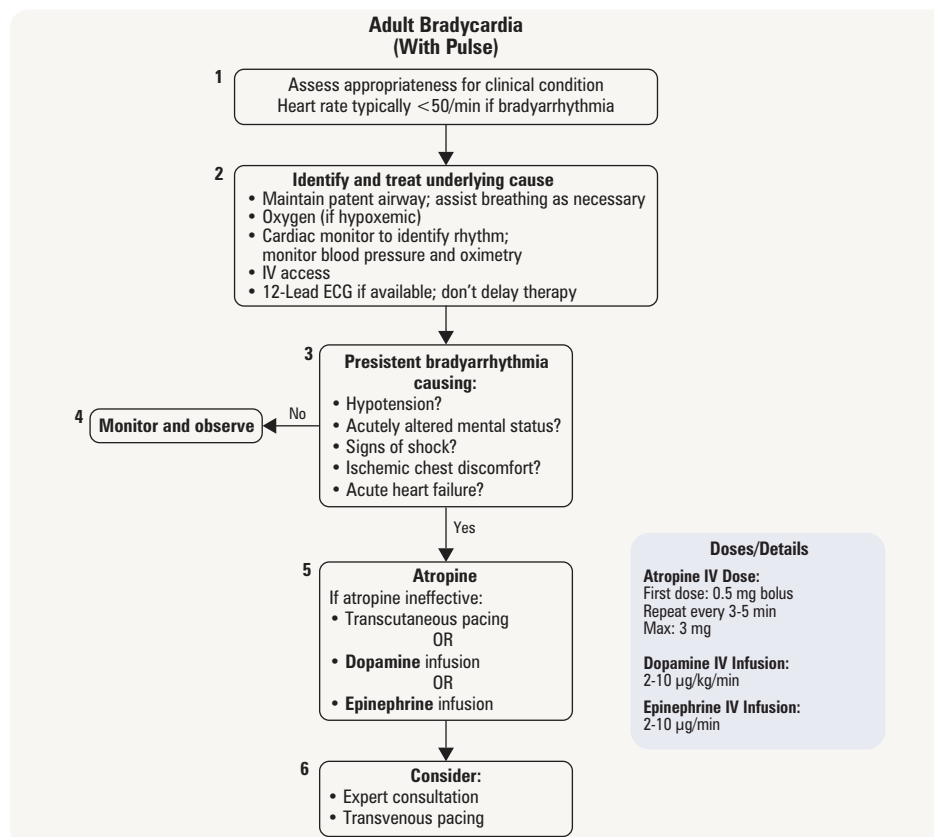


Figure 15. Adult bradycardia algorithm

Reprinted with permission: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Adult Advanced Cardiovascular Life Support. Circulation 2010;122[suppl 3]:S729-S767 ©2010 American Heart Association, Inc.

## References

- Arbous MS, et al. Impact of anesthesia management characteristics on severe morbidity and mortality. *Anesthesiology* 2005;102:257-268.
- Allain RM, et al. Clinical anesthesia procedures of the Massachusetts General Hospital, 8th ed. Philadelphia: Lippincott, 2010.
- Barash PG, et al. Clinical anesthesia, 6th ed. Philadelphia: Lippincott, 2009.
- Blanc VF, Tremblay NA. The complications of tracheal intubation: a new classification with review of the literature. *Anesth Analg* 1974;53:202-213.
- Carlisle J, Stevenson CA. Drugs for preventing post-operative nausea and vomiting. *Cochrane DB Syst Rev* 2006;Issue 3.
- Collins VJ. Physiologic and pharmacologic bases of anesthesia. Philadelphia: Lippincott, 1996.
- Craft TM, Upton PM. Key topics in anesthesia, clinical aspects, 3rd ed. Oxford: BIOS Scientific, 2001.
- Duke J. Anesthesia secrets, 4th ed. Philadelphia: Mosby, 2010.
- Ezekiel MR. Handbook of anesthesiology, 2002-2003 ed. Philadelphia: Current Clinical Strategies, 2001.
- Frank SM, et al. Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: a randomized clinical trial. *JAMA* 1997;277:1127-1134.
- Fleisher LA, et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation for noncardiac surgery: executive summary. *Circulation* 2007;116:1971-1996.
- Hebert PC, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *NEJM* 1999;340:409-417.
- Henderson JJ, et al. Difficult Airway Society guidelines for management of the unanticipated difficult intubation. *Anaesthesia* 2004;59:675-694.
- Hudcova J, et al. Patient controlled opioid analgesia versus conventional opioid analgesia for post-operative pain. *Cochrane DB Syst Rev* 2006;Issue 4.
- Kalant H, et al. Principles of medical pharmacology, 7th ed. New York: Oxford University Press, 2006.
- Bell RM, Dayton MT, Lawrence PF. Essentials of surgical specialties. Philadelphia: Lippincott, 2000. *Anesthesiology*; p.1-67.
- Lee A, Fan LTY. Stimulation of the wrist acupuncture point P6 for preventing post-operative nausea and vomiting. *Cochrane DB Syst Rev* 2009;Issue 2.
- Leighton BL, Halpern SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systemic review. *Am J Obstet Gynecol* 2002;186:569-577.
- Lette J, et al. Preoperative and long-term cardiac risk assessment predictive value of 23 clinical descriptors, 7 multivariate scoring systems, and quantitative dipyridamole imaging in 360 patients. *Ann Surg* 1992;216:192-204.
- Liccardi G, et al. Control of asthma for reducing the risk of bronchospasm in asthmatics undergoing general anesthesia and/or intravascular administration of radiographic contrast media. *Curr Med Res Opin* 2009;25:1621-1630.
- MacDonald NE, O'Brien SF, Delage G. Canadian Paediatric Society Infectious Diseases and Immunization Committee: Transfusion and risk of infection in Canada Update 2012. *Paediatr Child Health* 2012;17:e102-e111.
- Malignant Hyperthermia Association of the United States (internet). Available from <http://www.mhaus.org>. Accessed: Sept 26, 2010.
- Mangano DT, et al. Long-term cardiac prognosis following noncardiac surgery. *JAMA* 1992; 268:233-240.
- Mangano DT, et al. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *NEJM* 1996;335:1713-1720.
- Merchant R, et al. Guidelines to the practice of anesthesia, revised 2013 ed. *Can J Anaesth* 2013;60:60-84.
- Miller RD, et al. Miller's anesthesia, 7th ed. Philadelphia: Churchill Livingstone, 2000.
- Morgan GE, Mikhail MS, Murray MJ. Clinical anesthesiology, 4th ed. New York: McGraw-Hill Medical, 2005.
- Neumar RV, et al. American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care science. *Circulation* 2010;122:5729-5760.
- Palda VA, Detksy AS. Perioperative assessment and management of risk from coronary artery disease. *Ann Intern Med* 1997;127:313-328.
- Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane DB Syst Rev* 2012;Issue 4.
- POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE Trial): a randomized controlled trial. *Lancet* 2008;371:1839-1847.
- Poldermans D, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *NEJM* 1999;341:1789-1794.
- Posner KL, Van Norman GA, Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesth Analg* 1999;89:553-560.
- Rao TL, Jacobs KH, El-Etr AA. Reinfarction following anaesthesia in patients with myocardial infarction. *Anaesthesiology* 1983;59:499-505.
- Roberts JR, Spadafora M, Cone DC. Proper depth placement of oral endotracheal tubes in adults prior to radiographic confirmation. *Acad Emerg Med* 1995;2:20-24.
- Rodgers A, et al. Reduction of post-operative mortality and morbidity with epidural or spinal anesthesia: Results from overview of randomized trials. *BMJ* 2000;321:1-12.
- Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective betablockers for chronic obstructive pulmonary disease. *Cochrane DB Syst Rev* 2005;Issue 4.
- Salpeter SR, et al. Cardioselective betablockers for reversible airway disease. *Cochrane DB Syst Rev* 2002;Issue 4.
- Sessler DL. Complications and treatment of mild hypothermia. *Anesthesiology* 2001;95:531-543.
- Shiga T, et al. Predicting difficult intubation in apparently normal patients. *Anesthesiology* 2005;103:429-437.
- Sullivan P. Anesthesia for medical students. Ottawa: Doculink International, 1999.
- Yaphe J, Helman A (ed). The ABCs of emergency medicine, 11th ed. Toronto: University of Toronto, 2008. Circulation chapter, p8.
- Zwilling CW, et al. Complications of assisted ventilation. *Am J Med* 1974;57:161-170.



# Cardiology and Cardiovascular Surgery

Sangjune Laurence Lee and Bryan Ross, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Chi-Ming Chow, Dr. Michael McDonald, Dr. George Oreopoulos and Dr. Anna Woo, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	Coronary Revascularization	
		Percutaneous Coronary Intervention	
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	Coronary Artery Bypass Graft Surgery	
Coronary Circulation		Off Pump Coronary Artery Bypass Surgery	
Cardiac Anatomy			
<b>Differential Diagnoses of Common Presentations</b> . . . . .	<b>4</b>	<b>Heart Failure</b> . . . . .	<b>30</b>
Chest Pain		Congestive Heart Failure	
Loss of Consciousness		Sleep-Disordered Breathing	
Local Edema			
Generalized Edema		<b>Cardiac Transplantation</b> . . . . .	<b>34</b>
Palpitations		Ventricular Assist Devices	
Dyspnea			
<b>Cardiac Diagnostic Tests</b> . . . . .	<b>5</b>	<b>Myocardial Disease</b> . . . . .	<b>35</b>
Electrocardiography Basics		Myocarditis	
Approach to ECGs		Dilated Cardiomyopathy	
Rate		Hypertrophic Cardiomyopathy	
Rhythm		Restrictive Cardiomyopathy	
Axis			
Intraventricular Conduction Abnormalities		<b>Valvular Heart Disease</b> . . . . .	<b>38</b>
Hypertrophy and Chamber Enlargement		Infective Endocarditis	
Ischemia/Infarction		Rheumatic Fever	
Miscellaneous ECG Changes		Choice of Valve Prosthesis	
Cardiac Biomarkers		Summary of Valvular Disease	
Ambulatory ECG			
Echocardiography		<b>Pericardial Disease</b> . . . . .	<b>42</b>
Stress Testing		Acute Pericarditis	
Exercise Testing		Pericardial Effusion	
Nuclear Cardiology		Cardiac Tamponade	
Stress Echocardiography		Constrictive Pericarditis	
Indications for Stress Testing			
Cardiac Catheterization and Angiography		<b>VASCULAR DISEASE</b>	
Contrast-Enhanced CT Coronary Angiography		<b>Peripheral Arterial Disease</b> . . . . .	<b>44</b>
Magnetic Resonance Imaging		Peripheral Vascular Anatomy	
		Acute Arterial Occlusion/Insufficiency	
		Chronic Arterial Occlusion/Insufficiency	
<b>CARDIAC DISEASE</b>		<b>Hypertension</b> . . . . .	<b>FM37</b>
<b>Arrhythmias</b> . . . . .	<b>12</b>	<b>Pulmonary Hypertension</b> . . . . .	<b>R16</b>
Mechanisms of Arrhythmias			
Bradyarrhythmias		<b>Aortic Disease</b> . . . . .	<b>47</b>
AV Conduction Blocks		Aortic Anatomy	
Supraventricular Tachyarrhythmias		Aortic Dissection	
Pre-Excitation Syndromes		Aortic Aneurysm	
Ventricular Tachyarrhythmias			
Electrophysiology Studies		<b>Peripheral Venous Disease</b> . . . . .	<b>50</b>
Electrical Pacing		Deep Venous Thromboembolism	
Implantable Cardioverter Defibrillators		Superficial Venous Thrombosis	
Catheter Ablation		Varicose Veins	
		Chronic Venous Insufficiency	
<b>Ischemic Heart Disease</b> . . . . .	<b>22</b>	Lymphedema	
Chronic Stable Angina		<b>Common Medications</b> . . . . .	<b>53</b>
Variant Angina		Antiarrhythmics	
Syndrome X			
Acute Coronary Syndromes		<b>Landmark Cardiac Trials</b> . . . . .	<b>56</b>
Management of Acute Coronary Syndromes			
Treatment Algorithm for Chest Pain		<b>References</b> . . . . .	<b>58</b>
Sudden Cardiac Arrest			



## Acronyms

AAA	abdominal aortic aneurysm	CVD	cerebrovascular disease	LICS	left intercostal space	RBB	right bundle branch
ABI	ankle-brachial index	DCM	dilated cardiomyopathy	MI	myocardial infarction	RBBB	right bundle branch block
ACEI	angiotensin converting enzyme inhibitor	DM	diabetes mellitus	MPI	myocardial perfusion imaging	RBW	routine blood work
ACS	acute coronary syndrome	DVT	deep vein thrombosis	MR	mitral regurgitation	RVH	right ventricular hypertrophy
Afib	atrial fibrillation	ECASA	enteric coated ASA	MRA	MRI angiography	SEM	systolic ejection murmur
AR	aortic regurgitation	ECG	electrocardiogram	MS	mitral stenosis	STEMI	ST elevation myocardial infarction
ARB	angiotensin receptor blocker	Echo	echocardiogram	NSTEMI	non-ST elevation myocardial infarction	SVT	supraventricular tachycardia
ARDS	acute respiratory distress syndrome	EtOH	ethanol/alcohol	NSR	normal sinus rhythm	SCD	sudden cardiac death
AS	aortic stenosis	GERD	gastroesophageal reflux disease	OS	opening snap	SV	stroke volume
ASA	acetylsalicylic acid (Aspirin®)	HCM	hypertrophic cardiomyopathy	PCI	percutaneous coronary intervention	SVR	systemic vascular resistance
AV	atrioventricular	HTN	hypertension	PIV	posterior-interventricular artery	SLE	systemic lupus erythematosus
AVM	arteriovenous malformation	HR	heart rate	PND	paroxysmal nocturnal dyspnea	SA	sinoatrial
AVNRT	atrioventricular nodal re-entrant tachycardia	ICD	implantable cardiac defibrillator	PE	pulmonary embolism	SVT	supraventricular tachycardia
AVRT	atrioventricular re-entrant tachycardia	IE	infective endocarditis	PAC	premature atrial contraction	TAA	thoracic aortic aneurysm
BBB	bundle branch block	JVP	jugular venous pressure	PVC	premature ventricular contraction	TB	tuberculosis
BNP	brain natriuretic peptide	LA	left atrium	PDA	patent ductus arteriosus	TIA	transient ischemic attack
BP	blood pressure	LAE	left atrial enlargement	PFO	patent foramen ovale	TEE	transesophageal echocardiography
CABG	coronary artery bypass graft	LMWH	low molecular weight heparin	PUD	peptic ulcer disease	TTE	transthoracic echocardiography
CXR	chest x-ray	LVEF	left ventricular ejection fraction	PVD	peripheral vascular disease	UA	unstable angina
CAD	coronary artery disease	LBB	left bundle branch	RA	rheumatoid arthritis	VAD	ventricular assist device
CO	cardiac output	LBBB	left bundle branch block	RA	right atrium	VFib	ventricular fibrillation
CCB	calcium channel blocker	LV	left ventricle	RAE	right atrial enlargement	VT	ventricular tachycardia
CHF	congestive heart failure	LVH	left ventricular hypertrophy	RAO	right anterior oblique	VTE	venous thromboembolism
COPD	chronic obstructive pulmonary disease	LLSB	left lower sternal border	RV	right ventricle	WPW	Wolff-Parkinson-White
CTA	CT angiography						

## Basic Anatomy Review

### Coronary Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the root of the aorta (see Figure 1)
  - right coronary artery (RCA)
    - acute marginal branches
    - atrioventricular (AV) nodal artery
    - posterior interventricular artery (PIV) = posterior descending artery (PD)
  - left main coronary artery (LCA): two major branches
    - left anterior descending artery (LAD)
      - septal branches
      - diagonal branches
    - left circumflex artery (LC)
      - obtuse marginal branches
- dominance of circulation
  - right-dominant circulation: PIV and at least one posterolateral branch arise from RCA (80%)
  - left-dominant circulation: PIV and at least one posterolateral branch arise from LC (15%)
  - balanced circulation: dual supply of posteroinferior LV from RCA and LC (5%)
- the sinoatrial (SA) node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
- most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through Thebesian veins into all four chambers, contributing to the physiologic R-L shunt

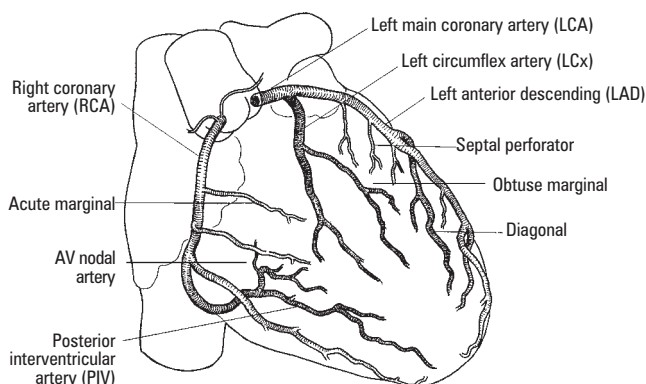


Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)

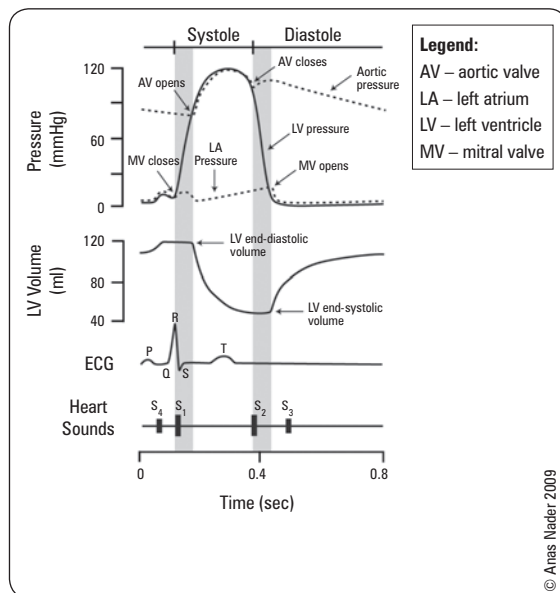


Figure 2a. Cardiac cycle

Grey shaded bars indicate isovolumic contraction (left) and isovolumic relaxation (right)

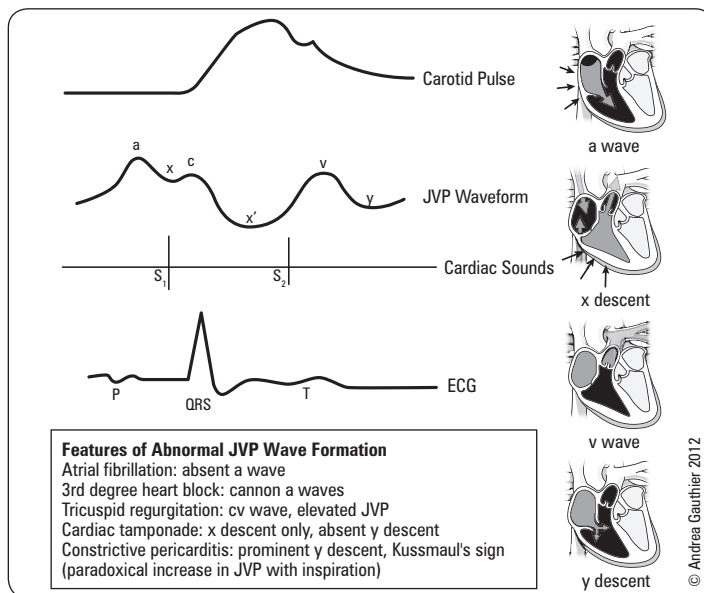


Figure 2b. JVP waveform

## Cardiac Anatomy

### • layers of the heart

- endocardium
- myocardium
- epicardium
- visceral pericardium
- pericardial cavity
- parietal pericardium

### • valves

- semilunar valves: no subvalvular apparatus present
  - ♦ aortic valve, 3 valve leaflets: separates LV and ascending aorta
  - ♦ pulmonic valve, 3 valve leaflets: separates RV and main pulmonary artery (PA)
- atrioventricular valves: subvalvular apparatus present in the form of chordae tendinae and papillary muscles
  - ♦ tricuspid valve, 3 valve leaflets: separates RA and RV
  - ♦ mitral valve, 2 valve leaflets: separates LA and LV

### • conduction system (see Figure 3)

- SA node governs pacemaking control
- anterior-, middle- and posterior-internal nodal tracts carry impulses in the right atrium and along Bachmann's bundle in the left atrium
- atrial impulses converge at the AV node
  - ♦ the AV node is the only conducting tract from the atria to the ventricles because of electrical isolation by the annulus fibrosis (except when accessory pathways are present)
- the bundle of His bifurcates into left and right bundle branches (LBB and RBB)
- LBB further splits into anterior and posterior fascicles
- RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium

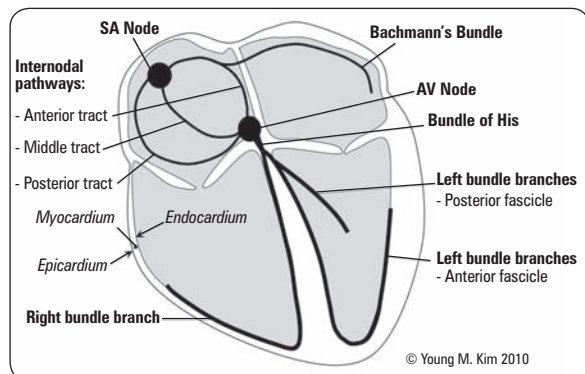


Figure 3. Conduction system of the heart

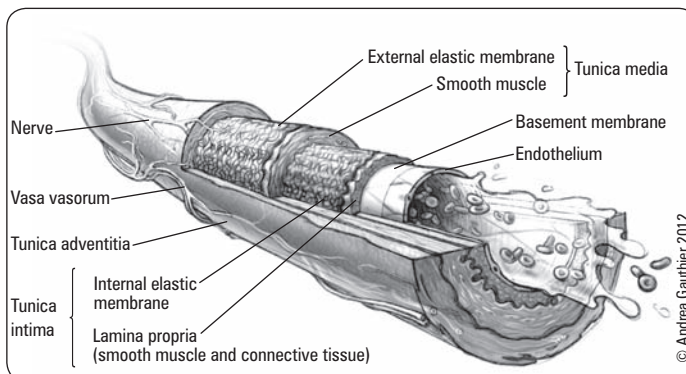


Figure 4. Blood vessel structure

- **cardiovascular innervation**

- sympathetic nerves
  - ♦ innervate the SA node, AV node, ventricular myocardium and vasculature
  - ♦ SA node ( $\beta_1$ ) fibres increase pacemaking activity (chronotropy)
  - ♦ cardiac muscle ( $\beta_1$ ) fibres increase contractility (inotropy) to help increase cardiac output
  - ♦ stimulation of  $\beta_1$ - and  $\beta_2$ -receptors in the skeletal and coronary circulation causes vasodilatation
- parasympathetic nerves
  - ♦ innervate the SA node, AV node, atrial myocardium but few vascular beds
  - ♦ basal vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node resulting in slowing of pacemaker activity and conduction (i.e. reduced dromotropy – if only affecting AV node conduction)
  - ♦ parasympathetics have very little impact on total peripheral vascular resistance

## Differential Diagnoses of Common Presentations

Note: **bold** text indicates most common, underlined text indicates life threatening

### Chest Pain

- cardiac
  - **MI/angina**
  - myocarditis
  - pericarditis/Dressler's syndrome
  - cardiac tamponade
- pulmonary
  - **pneumonia**
  - pulmonary embolism (PE)
  - pneumothorax/hemothorax, tension pneumothorax
  - empyema
  - pulmonary neoplasm
  - bronchiectasis
  - TB
- gastrointestinal
  - esophageal: spasm, **GERD**, esophagitis, ulceration, achalasia, neoplasm, Mallory-Weiss syndrome, esophageal rupture
- gastrointestinal
  - PUD
  - gastritis
  - pancreatitis
  - biliary colic
- mediastinal
  - lymphoma
  - thymoma
- vascular
  - dissecting aortic aneurysm
  - aortic rupture
- surface structures
  - costochondritis
  - rib fracture
  - skin (bruising, herpes zoster)
  - breast
- anxiety/psychosomatic

### Loss of Consciousness

- **hypovolemia**
- cardiac
  - structural or obstructive causes
    - ♦ acute coronary syndrome
    - ♦ aortic stenosis
    - ♦ hypertrophic cardiomyopathy (HCM)
    - ♦ cardiac tamponade, constrictive pericarditis
  - arrhythmias (see *Arrhythmias*, C12)
- respiratory
  - massive pulmonary embolism
  - pulmonary hypertension
  - hypoxia
  - hypercapnia
- neurologic
  - stroke/TIA (esp. vertebrobasilar insufficiency)
  - migraine
  - seizure
- metabolic
  - **anemia**
  - **hypoglycemia**
- drugs
  - antihypertensives
  - antiarrhythmics
  - diuretics
- **vasovagal**
- autonomic dysfunction
  - diabetic neuropathy
- psychiatric
  - panic attack

### Local Edema

- inflammation/infection
- venous or lymphatic obstruction
  - thrombophlebitis/deep vein thrombosis
  - venous insufficiency
  - chronic lymphangitis
  - lymphatic tumour infiltration
  - filariasis

### Generalized Edema

- increased hydrostatic pressure/fluid overload
  - **heart failure**
  - pregnancy
  - drugs (e.g. CCBs)
  - **iatrogenic** (e.g. IV fluids)
- decreased oncotic pressure/hypoalbuminemia
  - nephrotic syndrome
- **liver cirrhosis**
  - malnutrition
- increased capillary permeability
  - severe sepsis
- hormonal
  - hypothyroidism
  - exogenous steroids
  - pregnancy
  - estrogens

## Palpitations

- cardiac
  - **arrhythmias** (PAC, PVC, SVT, **VT**)
  - **valvular heart disease**
  - **hypertrophic cardiomyopathy (HCM)**
- endocrine
  - **thyrotoxicosis**
  - pheochromocytoma
  - hypoglycemia
- systemic
  - fever
  - **anemia**
- drugs
  - stimulants and anticholinergics
- psychiatric
  - panic attack

## Dyspnea

- cardiovascular
  - **acute MI**
  - **CHF/LV failure**
  - aortic/mitral stenosis
  - aortic/mitral regurgitation
  - arrhythmia
  - **cardiac tamponade**
  - constrictive pericarditis
  - left-sided obstructive lesions (e.g. left atrial myxoma)
  - elevated pulmonary venous pressure
- respiratory
  - airway disease
    - ♦ **asthma**
    - ♦ COPD exacerbation
    - ♦ upper airway obstruction (anaphylaxis, foreign body, mucus plugging)
  - parenchymal lung disease
    - ♦ **ARDS**
    - ♦ pneumonia
    - ♦ interstitial lung disease
- pulmonary vascular disease
  - ♦ **pulmonary embolism**
  - ♦ pulmonary HTN
  - ♦ pulmonary vasculitis
- pleural disease
  - ♦ pneumothorax
  - ♦ pleural effusion
- neuromuscular and chest wall disorders
  - C-spine injury
  - polymyositis, myasthenia gravis, Guillain-Barré syndrome
  - kyphoscoliosis
- anxiety/psychosomatic
- hematological/metabolic
  - anemia, acidosis, hypercapnia

## Cardiac Diagnostic Tests

### Electrocardiography (ECG) Basics

- the electrocardiogram (ECG) is a graphic representation of the electrical activity of the heart recorded from the surface of the body
- on the ECG graph
  - the horizontal axis represents time
    - ♦ 1 mm (1 small square) = 40 msec
    - ♦ 5 mm (1 large square) = 200 msec (at paper speed 25 mm/s)
  - the vertical axis represents voltage
    - ♦ 1 mm (1 small square) = 0.1 mV
    - ♦ 10 mm (2 large squares) = 1 mV (at standard gain setting)
- leads
  - standard 12-lead ECG
    - ♦ limb leads: I, II, III, aVL, aVR, aVF
    - ♦ precordial leads: V1-V6 (V1-V2 septal, V3-V4 anterior, V5-V6 lateral)
  - additional leads
    - ♦ right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
  - lateral = I, aVL, V5, V6; inferior = II, III, aVF; anterior = V1-V4

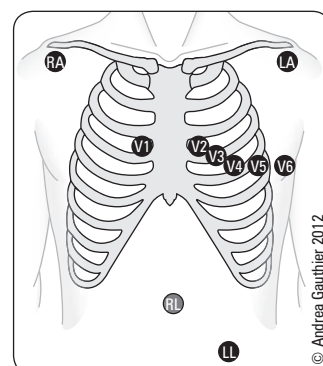


Figure 5. ECG lead placement

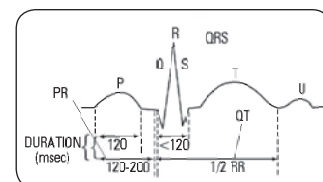


Figure 6. ECG waveforms and normal values

### Approach to ECGs

#### RATE

- normal = 60-100 bpm (atrial rate: 150-250 bpm = paroxysmal tachycardia, 250-350 bpm = atrial flutter, >350 bpm = AFib)
- regular rhythm
  - to calculate the rate, divide 300 by number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 s)
  - or remember 300-150-100-75-60-50-43 (rate falls in this sequence with the number of large squares between 2 QRS complexes)
- irregular rhythm
  - rate = 6 x number of R-R intervals in 10 s (the "rhythm strips" are 10 s recordings)
  - types: wandering pacemaker, multifocal atrial tachycardia, AFib
- atrial escape = 60-80 bpm; junctional escape = 40-60 bpm; ventricular escape = 20-40 bpm



#### Rate Calculations

- Examples, practice



#### Approach to ECGs Summary

- Rate
- Rhythm
- Axis
- Conduction
- Chamber enlargement/hypertrophy
- Ischemia/infarction
- Miscellaneous



For more examples and practice visit  
[www.ecgmadesimple.com](http://www.ecgmadesimple.com).

**RHYTHM**

- regular: R-R interval is the same across the tracing
- irregular: R-R interval varies across the tracing
- regularly-irregular: repeating pattern of varying R-R intervals
- irregularly-irregular: R-R intervals vary erratically
- normal sinus rhythm (NSR)
  - P wave precedes each QRS; QRS follows each P wave
  - P wave axis is normal (positive in leads I, aVF)
  - rate between 60-100 bpm

**AXIS**

- mean axis indicates the direction of the mean vector
- can be determined for any waveform (P, QRS, T)
- the standard ECG reported QRS axis usually refers to the mean axis of the anterior plane; it indicates the mean direction of ventricular depolarization forces
- QRS axis in the frontal plane (see Figure 7)
  - normal axis:  $-30^\circ$  to  $90^\circ$  (i.e. positive QRS in leads I and II)
  - left axis deviation (LAD): axis  $< -30^\circ$
  - right axis deviation (RAD): axis  $> 90^\circ$
- QRS axis in the horizontal plane is not routinely calculated; it is directed posteriorly and to the left
  - transition from negative to positive is usually in lead V3

**INTRAVENTRICULAR CONDUCTION ABNORMALITIES****Left Bundle Branch Block (LBBB)****Complete LBBB**

- QRS duration  $> 120$  msec
- Broad notched or slurred R waves in leads I, aVL and usually V5 and V6
- Deep broad S waves in leads V1-2
- Secondary ST-T changes (-ve in leads with broad R waves, +ve in V1-2) are usually present
- LBBB can mask ECG signs of MI

**Right Bundle Branch Block (RBBB)****Complete RBBB**

- QRS duration  $> 120$  msec
- Positive QRS in lead V1 (rSR' or occasionally broad R wave)
- Broad S waves in leads I, V5-6 ( $> 40$  msec)
- Usually secondary T wave inversion in leads V1-2

**Left Anterior Fascicular Block (LAFB) (Left Anterior Hemiblock)****Left axis deviation ( $-30^\circ$  to  $-90^\circ$ )**

- Small q and prominent R in leads I and aVL
- Small r and prominent S in leads II, III, and aVF

**Left Posterior Fascicular Block (LPFB) (Left Posterior Hemiblock)****Right axis deviation ( $110^\circ$  to  $180^\circ$ )**

- Small r and prominent S in leads I and aVL
- Small q and prominent R in leads II, III, and aVF

**Bifascicular Block****RBBB pattern**

- Small q and prominent R
- The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB
- Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks

**Nonspecific Intraventricular Block**

- QRS duration  $> 120$  msec
- absence of criteria for LBBB or RBBB

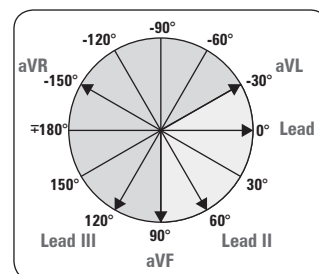
**Intervals**

PR	QRS	QT
Increased ( $> 200$ msec): <ul style="list-style-type: none"> <li>• Heart block</li> <li>• Atrial flutter</li> <li>• Sinus bradycardia</li> <li>• Hypokalemia</li> </ul>	Increased ( $> 120$ msec): <ul style="list-style-type: none"> <li>• Bundle branch block</li> <li>• Ventricular Tachycardia</li> <li>• Ventricular hypertrophy</li> <li>• WPW</li> <li>• Ectopic ventricular beat</li> <li>• Hyperkalemia</li> <li>• Drugs (e.g. TCAs, antiarrhythmics)</li> </ul>	Increased ( $QTc^* > 440$ msec): <ul style="list-style-type: none"> <li>• Genetic long QT syndrome</li> <li>• Drugs (e.g. antibiotics, SSRIs, anti-psychotics, antiarrhythmics)</li> <li>• Electrolyte disturbances (e.g. hypocalcemia, hypomagnesium, hypokalemia)</li> <li>• Hypothyroid</li> </ul>
Decreased ( $< 120$ msec): <ul style="list-style-type: none"> <li>• Pre-excitation syndrome (WPW)</li> </ul>		Decreased ( $QTc^* < 360$ msec) <ul style="list-style-type: none"> <li>• Hypercalcemia</li> <li>• Digoxin</li> <li>• Hyperthyroid</li> </ul>

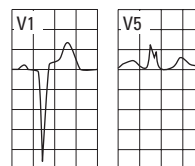
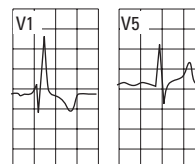
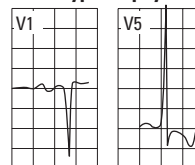
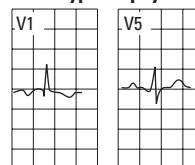
$QTc^* = QT \text{ interval} \div \sqrt{RR \text{ interval}}$

**Differential Diagnosis for Left and Right Axis Deviation**

LAD	RAD
Left ant. hemiblock	RVH
Inferior MI	Left post
WPW	hemiblock
RV pacing	PE
Normal variant	COPD
Elevated diaphragm	Lateral MI
Lead misplacement	WPW
Endocardial cushion defect	Dextrocardia
	Septal defects

**Figure 7. Axial reference system**

Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead results in an upward deflection in that lead. Normal QRS axis is between  $-30^\circ$  and  $+90^\circ$ .

**Left Bundle Branch Block****Right Bundle Branch Block****Left Ventricular Hypertrophy****Right Ventricular Hypertrophy**

© Paul Kelly 2011

**Figure 8. Complete LBBB, RBBB, LVH and RVH** (please see online examples for the full range of waveforms and the text for additional characteristics)



## HYPERTROPHY AND CHAMBER ENLARGEMENT

Left Ventricular Hypertrophy (LVH)	Right Ventricular Hypertrophy (RVH)
<ul style="list-style-type: none"> <li>S in V1 + R in V5 or V6 &gt;35 mm above age 40, (&gt;40 mm for age 31-40, &gt;45 mm for age 21-30)</li> <li>R in aVL &gt;11 mm</li> <li>R in I + S in III &gt;25 mm</li> <li>Additional criteria: <ul style="list-style-type: none"> <li>LV strain pattern (ST depression and T wave inversion in leads I, aVL, V4-V6)</li> <li>Left atrial enlargement</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Right axis deviation</li> <li>R/S ratio &gt;1 or qR in lead V1</li> <li>RV strain pattern: ST segment depression and T wave inversion in leads V1-2</li> </ul>
Left Atrial Enlargement (LAE)	Right Atrial Enlargement (RAE)
<ul style="list-style-type: none"> <li>Biphasic P wave with the negative terminal component of the P wave in lead V1 <math>\geq 1</math> mm wide and <math>\geq 1</math> mm deep</li> <li>P wave &gt;120 msec, notched in lead II ("P mitrale")</li> </ul>	<ul style="list-style-type: none"> <li>P wave &gt;2.5 mm in height in leads II, III, or aVF ("P pulmonale")</li> </ul>

## ISCHEMIA/INFARCTION

- look for the anatomic distribution of the following ECG abnormalities (see Table 1)
- ischemia
  - ST segment depression
  - T wave inversion (most commonly in V1-V6)
- injury
  - transmural (involving the epicardium): ST elevation in the leads facing the area injured/infarcted; transient ST elevation may occur in patients with coronary artery spasm (e.g. Prinzmetal angina) which can be slight or prominent (>10 mm)
  - subendocardial: marked ST depression in the leads facing the affected area; may be accompanied by enzyme changes and other signs of MI, may also occur with angina

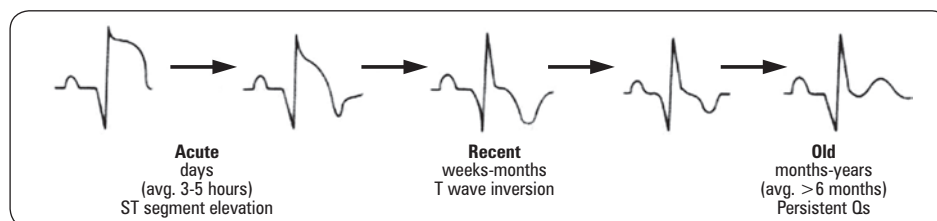
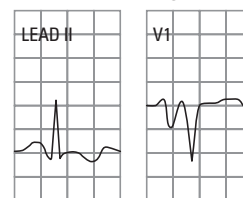


Figure 10. Typical ECG changes with infarction

- evolving infarction (ST elevation in contiguous leads = acute MI)
- "typical" sequential changes of evolving MI
  - hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
  - ST elevation (injury pattern) in the leads facing the infarcted area
    - usually in the first hours post infarct
    - in acute posterior infarction, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads, that are not recorded in the standard 12-lead ECG)
  - significant Q waves: >40 msec or >1/3 of the total QRS (hours to days post-infarct)
  - inverted T waves (one day to weeks after infarction)
    - this classical sequence does not always occur
    - Q waves of infarction may appear in the very early stages, with or without ST changes
    - non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction
- completed infarction
  - abnormal Q waves (wide Q waves may be found in III and aVL in normal individuals)
    - duration >40 msec (>30 msec in aVF for inferior infarction)
    - Q/QRS voltage ratio is >33%
  - abnormal R waves (R/S ratio >1, duration >40 msec) in V1 and more frequently in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)

### Left Atrial Enlargement



### Right Atrial Enlargement

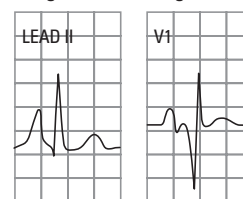


Figure 9. LAE, RAE (please see online examples and text above for characteristics)



### Significant ECG Changes

- Look for ST changes starting at 60 msec from J point
- J point = the junction between the QRS complex and the ST segment
- ST elevation: at least 1 mm in 2 adjacent limb leads, or at least 1-2 mm in adjacent precordial leads
- ST depression: downsloping or horizontal
- Q wave: pathological if Q wave  $\geq 1$  small square ( $\geq 40$  msec) or >33% of the total QRS



### Insignificant Q wave

- Septal depolarization by the left bundle
- Seen in leads I, II, III, aVL, V5, V6
- <40 msec



### Differential of ST Segment Changes

#### ST Elevation "I HELP A PAL"

Ischemia with reciprocal changes  
Hypothermia (Osborne waves)  
Early repolarization (normal variant; need old ECGs)  
LBBB  
Post-MI  
Acute STEMI  
Prinzmetal's (Vasospastic) angina  
Acute pericarditis (diffuse changes)  
Left/right ventricular aneurysm

#### ST Depression "WAR SHIP"

WPW syndrome  
Acute NSTEMI  
RBBB/LBBB  
STEMI with reciprocal changes  
Hypertrophy (LVH or RVH) with strain  
Ischemia  
Post-MI



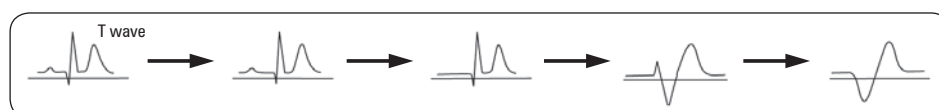
**Table 1. Areas of Infarction(Q wave)/Ischemia (in right dominant anatomy)**

Vessel Usually Involved	Infarct Area (LAD and LC)	Leads (LAD and LC)
Left anterior descending (LAD)	Anteroseptal	V1, V2
	Anterior	V3, V4
	Anterolateral	I, aVL, V3-6
	Extensive anterior	I, aVL, V1-6
Right coronary artery (RCA)	Inferior	II, III, aVF
	Right ventricle	V3R, V4R (right sided chest leads)
	Posterior MI (assoc. with inf. MI)	V1, V2 (prominent R waves)
Circumflex	Lateral	I, aVL, V5-6
	Isolated posterior MI	V1, V2 (prominent R waves)

## MISCELLANEOUS ECG CHANGES

### Electrolyte Disturbances

- hyperkalemia (see Figure 11)
  - mild to moderate ( $K^+$  5-7 mmol/L): tall peaked T waves
  - severe ( $K^+$  >7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show bizarre patterns, axis shifts left or right, ST shift with tall T waves
- hypokalemia (see Figure 12)
  - ST segment depression, prolonged QT interval, low T waves, prominent U waves (U>T)
  - enhances the toxic effects of digitalis
- hypercalcemia: shortened QT interval
- hypocalcemia: prolonged QT interval

**Figure 11. Hyperkalemia****Figure 12. Hypokalemia**

### Hypothermia

- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- AFib with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves (see Figure 13): “hump-like” waves at the junction of the J point and the ST segment

### Pericarditis

- early: diffuse ST segment elevation  $\pm$  PR segment depression, upright T waves
- later: isoelectric ST segment, flat or inverted T waves
- low voltage if chronic constrictive pericarditis
- tachycardia

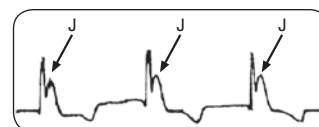
### Drug Effects

- digitalis
  - therapeutic levels may be associated with “digitalis effect” (see Figure 14):
    - ST downsloping or “scooping”
    - T wave depression or inversion
    - QT shortening  $\pm$  U waves
    - slowing of ventricular rate in AFib
  - toxic levels associated with:
    - arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradycardia in AFib, accelerated junctional rhythms, PVCs, ventricular tachycardia (see *Arrhythmias*, C12)
    - “regularization” of ventricular rate in AFib due to a junctional rhythm and AV dissociation
- amiodarone, quinidine, phenothiazines, tricyclic antidepressants, antipsychotics, some antihistamines, some antibiotics: prolonged QT interval, U waves



#### Low Voltage

- Definition: total QRS height in precordial leads <10 mm and limb leads <5 mm
- Differential diagnosis
  - Myocardial disease
    - Ischemia
    - Cardiomyopathy (usually infiltrative type), myocarditis
  - Pericardial effusion
  - Thick chest wall/barrel chest: COPD, obesity
  - Generalized edema
  - Hypothyroidism/myxedema
  - Inappropriate voltage standardization

**Figure 13. Osborne J waves of a hypothermic patient**

#### Digitalis Side Effects

Palpitations, fatigue, visual changes (yellow vision), decreased appetite, hallucinations, confusion and depression.



#### Quinidine

- Wide P wave
- Wide QRS
- Prolonged QT
- $\pm$  ST depression
- $\pm$  U wave

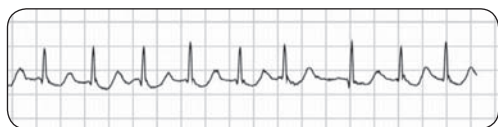


Figure 14. Atrial fibrillation, ST change due to digitalis ("digitalis effect")

### Pulmonary Disorders

- cor pulmonale (often secondary to COPD)
  - low voltage, RAD, poor R wave progression
  - RAE and RVH with strain
  - multifocal atrial tachycardia (MAT)
- massive PE
  - sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  - RAD, RVH with strain – most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III)



### Pacemakers

- Demand pacemaker has discharge (narrow vertical spike on ECG strip) prior to QRS
- Atrial pacemaker has discharge prior to P wave
- Triggered pacemaker has a discharge following the P wave but prior to the QRS
- Atrial and ventricular pacing have discharged before the P wave and QRS wave

## Cardiac Biomarkers

- provide diagnostic and prognostic information in acute coronary syndromes and in heart failure

Table 2. Cardiac Enzymes

Enzyme	Peak	Duration Elevated	DDx of Elevation
Troponin I, Troponin T	1-2 d	Up to 2 wk	MI, CHF, AFib, acute PE, myocarditis, chronic renal insufficiency, sepsis, hypovolemia
CK-MB	1 d	3 d	MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, etc.

- check troponin I at presentation and 8 h later  $\pm$  creatine kinase-MB (CK-MB; depends on local laboratory protocol)
- new CK-MB elevation can be used to diagnose reinfarction
- other biomarkers of cardiac disease:
  - AST and LDH also increased in MI (low specificity)
  - BNP and NT-proBNP: secreted by ventricles in response to increased end-diastolic pressure and volume
    - DDx of elevated BNP: CHF, AFib, PE, COPD exacerbation, pulmonary HTN

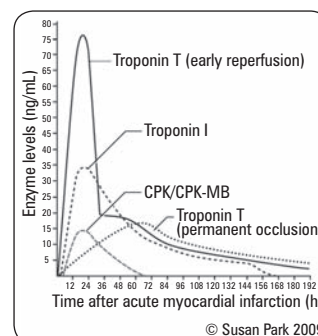


Figure 15. Cardiac enzymes



### Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea (BASEL)

NEJM 2004;350:647-54

Study: Prospective, RCT.

**Population:** 452 patients (mean age 71 yr. 58% male) with acute dyspnea; patients with severe renal disease or cardiogenic shock were excluded.

**Intervention:** Assessment including measurement of B-type natriuretic peptide or standard assessment.

**Outcome:** Time to discharge and total cost of treatment.

**Results:** Median time to discharge was significantly shorter in the intervention group when compared with the control group (8.0 vs. 11.0 d,  $p=0.001$ ). Total cost was also significantly lower in the intervention group (\$5410 vs. \$7264,  $p=0.006$ ). In addition, the measurement of B-type natriuretic peptide significantly reduced the need for admission to hospital and intensive care. The 30-d mortality rates were similar (10% vs. 12%,  $p=0.45$ ).

**Conclusions:** In patients with acute dyspnea, measurement of B-type natriuretic peptide improves clinical outcomes (need for hospitalization or intensive care) and reduces time to discharge and total cost of treatment.

## Ambulatory ECG

- indications for outpatient testing: palpitations, syncope, antiarrhythmic drug monitoring, arrhythmia surveillance in patients with documented or potentially abnormal rhythms, and surveillance of non-sustained arrhythmias that can lead to prophylactic intervention
- available technologies
  - Holter monitor
    - battery operated, continually records up to 3 leads for 24-48 h
    - symptoms recorded by patient on Holter clock for correlation with ECG findings
  - continuous loop recorder (diagnostic yield 66-83%)
    - worn continuously and can record data before and after patient activation for symptomatic episodes (usually worn for 2 wk)
  - external and implantable devices
    - external devices can be transtelephonically downloaded
    - implantable loop recorder (ILR): cannot be transtelephonically downloaded; left in place for 14 to 18 mo

## Echocardiography

### Transthoracic Echocardiography (TTE)

- ultrasound beams are directed across the chest wall to obtain images of the heart
- indications: evaluation of left ventricular ejection fraction (LVEF), wall motion abnormalities, myocardial ischemia and complications of MI, chamber size, wall thickness, valve morphology, proximal great vessel morphology, pericardial effusion, unexplained hypotension, murmurs, syncope, congenital heart disease
- use with Doppler to quantify degree of valvular stenosis or regurgitation

### Transoesophageal Echocardiography (TEE)

- ultrasound probe inserted into the esophagus to allow for better resolution of the heart and structures
- better visualization of posterior structures, including left atrium, mitral and aortic valves, interatrial septum
- invasive procedure used to complement transthoracic echocardiography
- indications: intracardiac thrombi, tumours, valvular vegetations (infective endocarditis), aortic dissection, aortic atheromas, prosthetic valve function, shunt, technically inadequate transthoracic study
- use with Doppler to quantify degree of valvular stenosis or regurgitation

### Stress Echocardiography

- echocardiography in combination with either physiologic (exercise treadmill or bike testing) or pharmacologic (dobutamine infusion) stress
- validated in demonstrating myocardial ischemia and assessing viability
- provides information on the global left ventricular response to exercise
- used for valvular heart disease evaluation

### Contrast Echocardiography

- contrast agents injected into the bloodstream to improve imaging of the heart
- conventional agent: agitated saline (contains microbubbles of air)
- allows visualization of right heart and intracardiac shunts, most commonly patent foramen ovale (PFO) and sometimes intrapulmonary shunt
- newer contrast agents are capable of crossing the pulmonary bed and achieving left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders and enhance evaluation of LV ejection fraction, wall motion abnormalities, and intracardiac mass

## Stress Testing

### EXERCISE TESTING

- cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring
- guidelines for use:
  - patients with intermediate (10-90%) pretest probability of CAD based on age, gender and symptoms
  - ST depression  $<1$  mm at rest, no left bundle branch block, no digoxin or estrogen use
- exercise test results stratify patients into risk groups:
  - low risk patients can be treated medically without invasive testing
  - intermediate risk patients may need additional testing in the form of exercise imaging studies or cardiac catheterization
  - high risk patients should be referred for cardiac catheterization

### Indications for Terminating Exercise Stress Test

- drop in systolic blood pressure of  $>10$  mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
- moderate to severe angina
- ST elevation ( $>1$  mm) in leads without diagnostic Q-waves (other than V1 or aVR)
- increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
- signs of poor perfusion (cyanosis or pallor)
- technical difficulties in monitoring ECG or systolic blood pressure
- patient's desire to stop
- sustained ventricular tachycardia

### Interpretation

- the most commonly used ECG criteria for a positive exercise test:  $\geq 1$  mm of horizontal or downsloping ST-segment depression or elevation (at least 60 to 80 msec after the end of the QRS complex)

### NUCLEAR CARDIOLOGY

- myocardial perfusion imaging (MPI) with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
- evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously
- predicts the likelihood of further cardiac event rates independent of the patient's history, examination, resting ECG, and stress ECG
- often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi)
- stress with either treadmill or IV vasodilator stress [dipyridamole (Persantine®), adenosine]
- images of the heart obtained during stress and at rest 3-4 h later
  - fixed defect: impaired perfusion at rest and during stress (infarcted/hibernating)
  - reversible defect: impaired perfusion only during stress (ischemic)



#### Most Commonly Used Treadmill Stress Test Protocols

- **The Bruce Protocol:** 7 stage test with each stage lasting 3 min. With each successive stage, the treadmill increases in both speed and gradient
- **The Modified Bruce, Modified Naughton Protocol:** for older individuals or those with limited exercise capacity



#### Important Contraindications to Exercise Testing

- Acute MI, aortic dissection, pericarditis, myocarditis, PE
- Severe AS, arterial HTN
- Inability to exercise adequately



#### Important Prognostic Factor Duke Treadmill Score (DTS) Weighted Index Score:

- Treadmill exercise time using standard Bruce protocol
- Maximum net ST segment deviation (depression or elevation)
- Exercise-induced angina provides diagnostic and prognostic information (such as 1-yr mortality)

$$DTS = \text{exercise time} - (5 \times \text{MaxST}) - (4 \times \text{angina index})$$

Ann Intern Med 1987;106:793-800



Patients with normal imaging (nuclear perfusion or stress echo) studies at peak stress have a  $<1\%$ /yr incidence of death or nonfatal MI and are thus often spared further invasive evaluation.

- tracers
  - thallium-201 ( $^{201}\text{Tl}$ , a  $\text{K}^+$  analogue)
  - technetium-99 ( $^{99}\text{Tc}$ )-labelled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®)

### STRESS ECHOCARDIOGRAPHY

- see *Stress Echocardiography*, C10

### INDICATIONS FOR STRESS TESTING

- exercise ECG
  - initial evaluation in patients who are able to exercise
- exercise stress echo
  - when ECG is uninterpretable
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - post-ACS when used to decide on potential efficacy of revascularization
  - to evaluate the clinical significance of valvular heart disease
- dobutamine stress echo (DSE)
  - among patients unable to exercise; same indications as exercise stress echo
  - low dose DSE can be used to assess myocardial viability and for assessing aortic stenosis with LV systolic dysfunction
- exercise MPI
  - when ECG is uninterpretable
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - in patients with previous imaging whose symptoms have changed
  - to diagnose ischemia
- dipyridamole/adenosine MPI
  - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarkers
  - when ECG is uninterpretable due to LBBB or V-paced rhythm
  - among patients unable to exercise, with the same indications as exercise MPI



#### ACC/AHA 2009 Guidelines for Use of Nuclear Testing

Stable angina, baseline ECG abnormalities, post-revascularization assessment, heart failure, patients unable to exercise, preoperative risk assessment for patients undergoing noncardiac surgery.



#### Sensitivity and Specificity of Various Stress Testing

- Exercise ECG (Sn 68; Sp 77)
- Stress Echocardiography (Sn 76; Sp 88)
- PET scanning (Sn 91; Sp 82)
- MIBI scanning (Sn 88; Sp 77)

## Cardiac Catheterization and Angiography

- risks of procedure related complications: vascular injury, renal failure, stroke, MI
- mortality rate 0.1-0.2%
- invasive: catheters are introduced percutaneously into arterial and venous circulation under conscious sedation and contrast is injected
- arterial access most commonly through the femoral artery; radial approach gaining favour especially for obese patients and outpatients dependent on driving and ambulation
- venous access through the femoral vein or internal jugular vein
- same day procedure as outpatient
  - indications for prehospitalization: anticoagulation, renal failure, diabetes, contrast allergy
- catheterization permits direct measurement of intracardiac pressures, transvalvular and mean peak pressure gradients, valve areas, cardiac output, shunt data, oxygen saturations, and visualization of coronary arteries, cardiac chambers and great vessels
- angiography may provide valuable information regarding lesion severity, complexity, location and prognosis

### Right Heart Catheterization (Swan-Ganz Catheter)

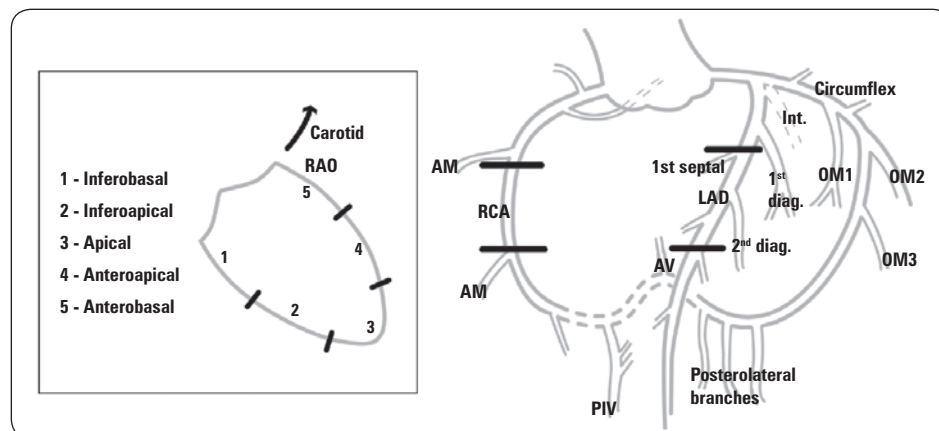
- right atrial, right ventricular, and pulmonary artery pressures are recorded
- pulmonary capillary wedge pressure (PCWP)
  - obtained by advancing the catheter to wedge in the distal pulmonary artery
    - ♦ records pressure measured from the pulmonary venous system
    - ♦ in the absence of pulmonary venous disease reflects left atrial pressure

### Left Heart Catheterization

- systolic and end-diastolic pressure tracings recorded; LV size, wall motion and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
- cardiac output (measured by the Fick oxygen method or the indicator dilution method)

### Coronary Angiography

- coronary vasculature accessed via the coronary ostia
- contraindicated in severe renal failure (due to contrast agent toxicity) must check renal status



**Figure 16. Coronary angiogram schematic** (RCA = right coronary artery; AM = acute marginal; LAD = left anterior descending; OM = obtuse marginal)

### Diagnostic Catheterization

- complications for diagnostic catheterization <1%
- inadequate diagnostic procedures occur in fewer than 1% of cases
- provocative pharmacological agents can be used to unmask pathology
  - fluid loading may unmask latent pericardial constriction
  - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in HCM
  - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  - a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, calcium channel blockers, adenosine, nitric oxide, or prostacyclin)



#### ACC/AHA 2011 Recommended Indications for Coronary Angiography

- Disabling (CCS classes III and IV) chronic stable angina despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Serious ventricular arrhythmia or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing



#### Coronary Angiography

Gold standard for localizing and quantifying CAD.



Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter.

## Contrast-Enhanced CT Coronary Angiography

- fast ECG-synchronized multi-slice CT image acquisition in the heart has enabled non-invasive imaging of the coronary arterial tree
- often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
- sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis

## Magnetic Resonance Imaging (MRI)

- offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
- valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, and assessment of viable myocardium

## CARDIAC DISEASE

## Arrhythmias



## Mechanisms of Arrhythmias

### (I) Alterations in Impulse Formation

#### A. Abnormal Automaticity

- automaticity is a property of certain cardiomyocytes to depolarize to their threshold voltage to spontaneously generate action potentials in a rhythmical fashion
- under normal circumstances only cells in the specialized conduction system (SA node, AV node and ventricular conduction system) exhibit natural automaticity. These cells are pacemaking cells. The automaticity of these cells can become abnormally increased or decreased

- in disease (e.g. post-MI ventricular ischemia) cells in the myocardium outside the conduction system may inappropriately acquire the property of automaticity and contribute to abnormal depolarization. If these ectopic generators depolarize at a rate that is greater than the SA node, they assume pacemaking control and become the source of abnormal rhythm
- automaticity can be influenced by:
  - neurohormonal tone (sympathetic and parasympathetic stimulation)
  - abnormal metabolic conditions (hypoxia, acidosis, hypothermia)
  - electrolyte abnormalities
  - drugs (e.g. digitalis)
  - local ischemia/infarction
  - other cardiac pathology
- this mechanism is responsible for the accelerated idioventricular rhythm and ventricular tachycardia that often occurs 24 to 72 h post MI

## B. Triggered Activity due to Afterdepolarizations

### 1. Early Afterdepolarizations

- occur in the context of action potential prolongation
- consequence of the membrane potential becoming more positive during repolarization
- result in self-maintaining depolarizing oscillations of action potential, generating a tachyarrhythmia
- basis for the degeneration of QT prolongation, either congenital or acquired, into Torsades de Pointes

### 2. Delayed Afterdepolarizations

- occur after the action potential has fully repolarized, but before the next usual action potential, thus called a delayed afterdepolarization
- commonly occurs in situations of high intracellular calcium (digitalis intoxication, ischemia) or during enhanced catecholamine stimulation

## (II) Alterations in Impulse Conduction

### A. Re-Entry Circuits

- the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium
  - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits

### B. Conduction Block

- ischemia, fibrosis, trauma, and drugs can cause transient, permanent, unidirectional or bidirectional block
- most common cause of block is due to refractory myocardium (cardiomyocytes are in refractory period or zone of myocardium unexcitable due to fibrosis)
- if block occurs along the specialized conduction system distal zones of the conduction system can assume pacemaking control
- conduction block can lead to bradycardia or tachycardia when impaired conduction leads to re-entry phenomenon

### C. Bypass Tracts

- normally the only conducting tract from the atria to the ventricles is the AV node
- congenital/acquired accessory conducting tracts bypass the AV node and facilitate premature ventricular activation before normal AV node conduction
- see *Pre-Excitation Syndromes*, C18

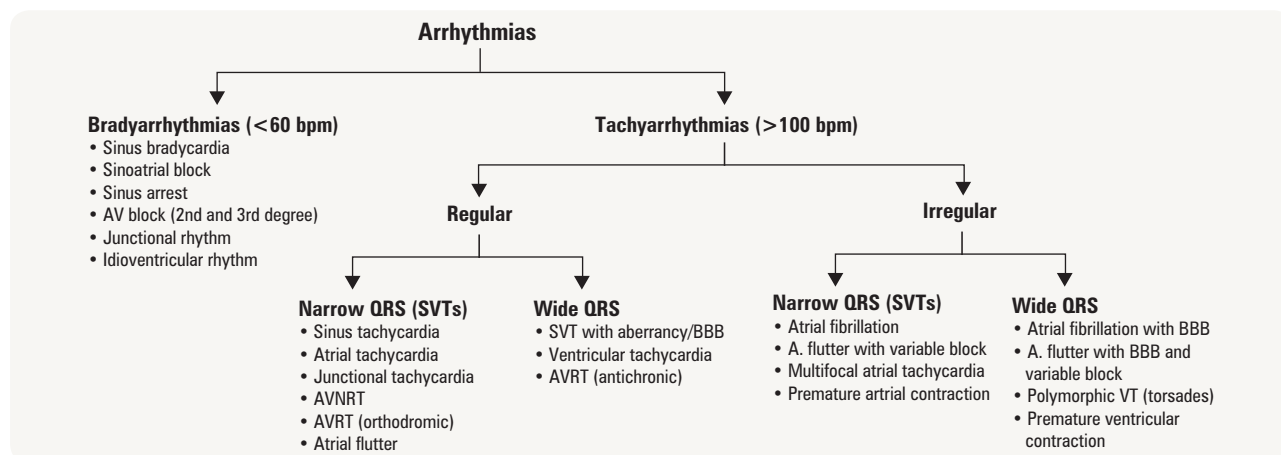


Figure 17. Clinical approach to arrhythmias



## Bradyarrhythmias



### Bradyarrhythmias

- Examples

### SA NODAL DYSFUNCTION

#### Sinus Bradycardia

- P axis normal (P waves positive in I and aVF)
- rate <60 bpm
- marked sinus bradycardia (<50 bpm) may be seen in normal adults, particularly athletes, and in elderly individuals
- caused by
  - increased vagal tone or vagal stimulation
  - vomiting
  - episodes of myocardial ischemia or infarction (inferior MI)
  - sick sinus syndrome
  - increased intracranial pressure
  - hypothyroidism
  - hypothermia
  - drugs (β-blockers, calcium channel blockers, etc.)
- treatment: if symptomatic, atropine during acute episodes; pacing for sick sinus syndrome; if drug-induced, reduction or withdrawal of drugs

#### Sinus Block, Pause, and Arrest

- three disorders involving the SA node; the sinus pacemaker fires but the impulse fails to depolarize the atrial myocardium resulting in no initial P wave (and consequently no QRS complex, ST segment, or T wave)
- sinus block (SA block), a complete block or failure of the sinus node to depolarize the atria; the block can last one or more cardiac cycles and is a multiple of the normal P-P interval
- sinus pause: a delay in the formation of a sinus impulse in the SA node resulting in a temporary pause (usually >3 s)
- sinus arrest: a longer delay in the formation of a sinus impulse in the SA node
  - there is no clear cut-off between sinus pause vs. arrest – if the pause lasts greater than 3x the normal P-P interval then it may be called an arrest
  - the P-P prolongation is not phasic or gradual (unlike sinus arrhythmia) and is not a multiple of the normal P-P interval (unlike sino-atrial block)
- escape beats or rhythm may occur:
- atrial escape: P waves with abnormal morphology
- junctional escape: P waves not seen, or follow the QRS (retrograde P), rate 40-60 bpm
- ventricular escape: no P wave; wide, abnormal QRS; slow rate 20-40 bpm

#### Sick Sinus Syndrome

- characterized by sinus node dysfunction (marked bradycardia, sinus pause/arrest, sinoatrial block)
  - when symptomatic, electronic pacemaker is indicated
- frequently associated with episodes of atrial tachyarrhythmias (“tachy-brady syndrome”)
- usually require a combination of a pacemaker for bradycardia and medications (β-blocker, calcium channel blocker, and/or digoxin, initiated after pacemaker insertion) for tachycardia



#### Sinus Arrhythmia (SA)

- Normal P waves, with variation of the P-P interval by >120 msec due to varying rate of SA node

#### Respiratory SA

- Seen more often in young adults (<30 yr old)
- Normal, results from changes in autonomic tone during respiratory cycle
- Rate increases with inspiration, slows with expiration

#### Non-respiratory SA

- Seen more often in the elderly
- Can occur in the normal heart; if marked may be due to sinus node dysfunction (e.g. in heart disease, or after digitalis toxicity)
- Usually does not require treatment

## AV Conduction Blocks

#### First Degree AV Block

- prolonged PR interval (>200 msec)
- frequently found among otherwise healthy adults
- no treatment required

#### Second Degree AV Block

- some of the atrial impulses are not conducted to the ventricles
- can describe block by ratio of number of P waves to number of QRS (e.g. 2:1, 3:1, 4:1 increases in severity)
- second degree AV block is further subdivided into Type I and Type II block:
  - Type I (Mobitz I) second degree AV block
    - ♦ a gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
    - ♦ AV block is usually in AV node (proximal)
      - triggers (usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia
      - not an indication for temporary or permanent pacing

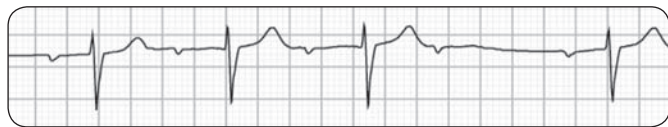


Figure 18. Second degree AV block with Wenckebach phenomenon (Mobitz I) (4:3 conduction) (lead V<sub>1</sub>)

- Type II (Mobitz II) second degree AV block
  - ♦ the PR interval is constant; there is an abrupt failure of conduction of a P wave
  - ♦ AV block is usually distal to the AV node (i.e. His bundle)
  - ♦ increased risk of high grade or 3rd degree AV block

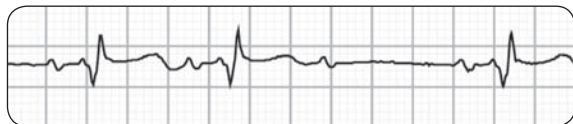


Figure 19. Second degree AV block (Mobitz II) (3:2 conduction) (lead V<sub>1</sub>)

### 2:1 AV Block

- often not possible to determine whether the block is type I or type II
- prolonged or repeated recordings may clarify the diagnosis

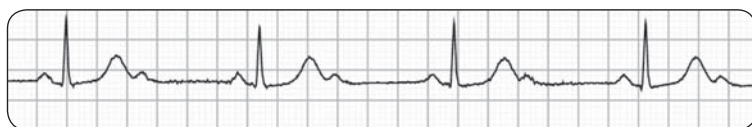


Figure 20. 2:1 AV block (lead II)

### Third Degree AV Block

- complete failure of conduction of the supraventricular impulses to the ventricles
- ventricular depolarization initiated by an escape pacemaker distal to the block
- QRS can be narrow or wide (junctional vs. ventricular escape rhythm)
- P-P and R-R intervals are constant, variable PR intervals
- no relationship between P waves and QRS complexes (P waves “marching through”)
- management (see *Electrical Pacing*, C21)



Figure 21. Third degree AV block (complete heart block) (lead II)

## Supraventricular Tachyarrhythmias



**Tachyarrhythmias**  
• Examples

### Presentation for SVT (and pre-excitation syndromes)

- presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate congestive heart failure (CHF), hypotension or ischemia in patients with underlying disease
- untreated tachycardias can cause cardiomyopathy (rare, potentially reversible with treatment of SVTs)
- includes supraventricular and ventricular rhythms

### Supraventricular Tachyarrhythmias (SVT)

- tachyarrhythmias that originate in the atria or AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS, unless there is pre-existing bundle branch block or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

### Sinus Tachycardia

- sinus rhythm with rate >100 bpm
- occurs in normal subjects with increased sympathetic tone (exercise, emotions, pain), alcohol use, caffeinated beverages, drugs (e.g.  $\beta$ -adrenergic agonists, anticholinergic drugs, etc.)
- etiology: fever, hypotension, hypovolemia, anemia, thyrotoxicosis, CHF, MI, shock, PE, etc.
- treatment: treat underlying disease; consider  $\beta$ -blocker if symptomatic, calcium channel blocker if  $\beta$ -blockers contraindicated

### Premature Beats

- premature atrial contraction (PAC) (Figure 27)
  - ectopic supraventricular beat originating in the atria
  - P wave morphology of the PAC usually differs from that of a normal sinus beat
- junctional premature beat
  - ectopic supraventricular beat that originates in the vicinity of the AV node
  - P wave is usually not seen or an inverted P wave is seen and may be before or closely follow the QRS complex
- treatment usually not required

### Atrial Flutter

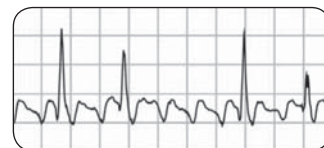
- rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly the right atrium)
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (2:1, 3:1, 4:1, etc.) or variable
- etiology: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis
- ECG: sawtooth flutter waves (most common type of flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy) (see Figure 22)
- in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and bring out flutter waves
- treatment
  - acute: if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable
    - rate control:  $\beta$ -blocker, diltiazem, verapamil, or digoxin
    - chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
  - anticoagulation guidelines same as for patients with AFib (see *Atrial Fibrillation*, below)
  - long-term: antiarrhythmics, catheter radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter)

### Multifocal Atrial Tachycardia (MAT)

- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
- atrial rate 100-200 bpm; at least 3 distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
- occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil),  $\beta$ -blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics or ablation

### Atrial Fibrillation (AFib)

- see *CCS Atrial Fibrillation Guidelines 2012* for details (free mobile apps available on iOS, Android and Blackberry)
- most common sustained arrhythmia
- incidence increases with age (10% of population >80 yr old)
- symptoms: palpitations, fatigue, syncope, may precipitate or worsen heart failure
- classification:
  - chronic/permanent: continuous atrial fibrillation that is unresponsive to cardioversion; cardioversion will not be reattempted
  - lone: occurs in persons younger than 60 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease, prosthetic heart valves, or valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: atrial fibrillation sustained for more than 7 d or atrial fibrillation that terminates only with cardioversion
  - recurrent: two or more episodes of atrial fibrillation
  - secondary: caused by a separate underlying condition or event (e.g. myocardial infarction, cardiac surgery, pulmonary disease, hyperthyroidism)
  - may be associated with thromboembolic events (4%/yr in nonvalvular AFib)
- initiation
  - single circuit re-entry and/or ectopic foci act as aberrant generators producing atrial tachycardia (350-600 bpm)
  - impulses conduct irregularly across the atrial myocardium to give rise to fibrillation
  - in some cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated
- maintenance
  - the tachycardia causes atrial structural and electrophysiological remodelling changes that further promote AFib; the longer the patient is in AFib the more difficult it is to convert back to sinus rhythm
- consequences
  - the AV node irregularly filters incoming atrial impulses producing an irregular ventricular response of <200 bpm and the tachycardia leads to suboptimal cardiac output
  - fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation – AFib is an important risk factor for stroke



**Figure 22. Atrial flutter with variable block**



#### CHA2DS2-VASc Score

The European Society of Cardiology (ESC) and the Canadian Cardiovascular Society (CCS) have incorporated the Birmingham 2009 schema (CHA2DS2-VASc) for the prediction of stroke risk in latest guidelines. The CHADS2 (Table 3) score is to be applied first; followed by the VASc schema if the score is <2 to further grade the risk of stroke in patients at low risk. A score of 0 indicates the patient is very low risk of stroke and may require either ASA alone or no antithrombotic therapy, with the latter preferred. A score of 1 indicates the utility of either ASA or an oral anticoagulant, with the latter preferred. A patient with a score of  $\geq 2$  should receive an oral anticoagulant. For more information, please see **Focused 2012 Update of the CCS AF Guidelines**, *Can J Cardiol* 2012;28:125-136.



#### Rivaroxaban for Stroke Prevention in Atrial Fibrillation – ROCKET-AF Trial

*NEJM* 2011;365:883-891

**Study:** Prospective, non-inferiority, double blind, RCT, median follow-up of 1.9 yr.

**Population:** 14,264 patients with atrial fibrillation (mean CHADS2 = 3.5). Patients either had previous thromboembolism or  $\geq 3$  risk factors.

**Intervention:** Patients were randomized to receiving rivaroxaban or warfarin.

**Outcome:** Composite of strokes and systemic thromboembolic event (STE).

**Results:** The hazard ratio of the primary outcome for rivaroxaban compared to warfarin was 0.88; 95% CI, 0.74-1.03;  $P < 0.001$  for noninferiority;  $P = 0.12$  for superiority. Furthermore, the hazard ratio for major and non-major, but clinically relevant, bleeding was 1.03; 95% CI, 0.96-1.11;  $P = 0.44$ . There were also significant reductions in intracranial hemorrhage (0.5% vs. 0.7%,  $P = 0.02$ ) and fatal bleeding (0.2% vs. 0.5%,  $P = 0.003$ ) for rivaroxaban.

**Conclusions:** In patients with atrial fibrillation, rivaroxaban is non-inferior to warfarin for stroke prevention and major and non-major bleeding.

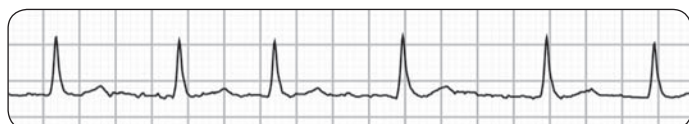
**Table 3. CHADS2 Risk Prediction for Non-Valvular AFib**

Risk Factor	Points	CHADS2 Score	Stroke Risk (%/Yr)	Anticoagulation Recommendation
Congestive Heart Failure	1	0	1.9 (low)	ASA 81-325 mg OD
Hypertension	1	1	2.8 (low -mod)	oral anticoagulants*
Age >75	1	2-3	4.0-5.9 (mod)	oral anticoagulants*
Diabetes	1	4-6	8.5-18.2 (high)	oral anticoagulants*
Stroke/TIA (prior)	2			

JAMA 2001;285:2864-70 and Canadian Journal of Cardiology 2012;28:125-136  
 Oral anticoagulants \* currently includes warfarin (INR 2-3), dabigatran, rivaroxaban

### AFib on ECG

- no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline
- irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
- wide QRS complexes due to aberrancy may occur following a long-short cycle sequence ("Ashman phenomenon")
- loss of atrial contraction, thus no "a" wave seen in JVP, no S4 on auscultation

**Figure 23. Atrial fibrillation (lead II)**

### Management (adapted from CCS Atrial Fibrillation Guidelines 2012)

**Major objectives (RACE):** all patients with AF (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk and for the risk of bleeding, and most patients should receive either an oral anticoagulant or ASA (see Table 3)

1. Rate control:  $\beta$ -blockers, diltiazem, verapamil (in patients with heart failure: digoxin, amiodarone)
2. Anticoagulation: use either warfarin, dabigatran, rivaroxaban, apixaban to prevent thromboembolism
3. Cardioversion (electrical)
  - if AFib <24-48 h, can usually cardiovert without anticoagulation
  - if AFib >24-48 h, anticoagulate for 3 wk prior and 4 wk after cardioversion
  - if patient unstable (hypotensive, active angina due to tachycardia, uncontrolled heart failure) should cardiovert immediately
4. Etiology
  - HTN, CAD, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, post-operative, PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol ("holiday heart")
  - may present in young patients without demonstrable disease ("lone AFib") and in the elderly without underlying heart disease

### Additional Management Points Regarding AFib

- studies of patients with AFib suggest that there is no difference in long-term survival when treating patients with a rhythm-control versus rate-control strategy
- however, many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate AFib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible

### Newly Discovered AFib

- anticoagulants may be beneficial if high risk for stroke
- if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
- if AFib persists, 2 options:
  1. rate control and anticoagulation (as indicated above)
  2. cardioversion (as above)

### Recurrent AFib/Permanent AFib

- if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
- patients who have undergone at least one attempt to restore sinus rhythm may remain in AFib after recurrence: permanent AFib may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations



#### Atrial Fibrillation – AFFIRM Trial

NEJM 2002;347:1825-1833

**Study:** Randomized, multicenter trial with mean follow-up of 3.5 yr.

**Population:** 4060 patients (mean age 70 yr, 61% male, 89% white) with AF and a high risk of stroke or death.

**Intervention:** Rate control ( $\beta$ -blockers, calcium channel blockers, or digoxin alone or in combination) vs. rhythm control (antiarrhythmic drug chosen by the treating physician).

**Primary Outcome:** All cause mortality.

**Results:** There was no difference in mortality or disabling stroke, anoxic encephalopathy, major bleeding, and cardiac arrest between the two groups. There were more incidents of hospitalizations (80.1% vs. 73%,  $p < 0.001$ ) and adverse events (Torsades de Pointes (12 vs. 2,  $p = 0.007$ ), pulseless or bradycardic arrest (9 vs. 1,  $p = 0.01$ ), pulmonary event (108 vs. 24,  $p < 0.001$ ), gastrointestinal event (127 vs. 35,  $p < 0.001$ ), prolonged QT interval (31 vs. 4,  $p \leq 0.001$ ), bradycardia (105 vs. 64,  $p = 0.001$ ) in the rhythm-control group.

**Conclusion:** Rate-control was as effective as rhythm-control in AF and was better tolerated. There were more hospitalization incidents in the rhythm-control group.



#### Oral Anticoagulants versus Antiplatelet Therapy for Preventing Stroke in Patients with Non-Valvular Atrial Fibrillation and No History of Stroke or Transient Ischemic Attacks

Cochrane DB Syst Rev 2009;3:CD006186

**Study:** Cochrane DB Syst Rev 8 RCTs with mean 1.9 yr of follow-up.

**Population:** 9598 total patients with non-valvular AF and no history of stroke or transient ischemic attack.

**Intervention:** Long-term adjusted-dose warfarin versus ASA (dose ranging from 75 to 325 mg).

**Outcome:** All cause mortality, all stroke, vascular death, MIs.

**Results:** Dose-adjusted warfarin therapy significantly reduced all stroke (OR 0.68, 95% CI 0.54-0.85), ischemic stroke (OR 0.53, 95% CI 0.41-0.68), and systemic emboli risk (OR 0.48, 95% CI 0.25-0.90). There was no significant difference in disabling or fatal strokes, MI, vascular death or all cause mortality. There was a significantly increased risk of intracranial hemorrhage with warfarin therapy versus ASA (OR 1.98, 95% CI 1.20-3.28).

**Conclusion:** Long-term adjusted-dose warfarin significantly reduces all stroke and embolic risks but does not reduce risk of disability or mortality and carries a significant intracranial hemorrhage risk. The threshold of benefit for anticoagulation versus antiplatelet therapy remains controversial.



- if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
  - no or minimal heart disease: flecainide, propafenone or sotalol
  - LV dysfunction: amiodarone
  - CAD:  $\beta$ -blockers, amiodarone

### AV Nodal Re-Entrant Tachycardia (AVNRT)

- re-entrant circuit using dual pathways (fast conducting  $\beta$ -fibres and slow conducting  $\alpha$ -fibres) within or near the AV node; often found in the absence of structural heart disease – cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset
- fast regular rhythm: rate 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex (see Figure 24)
- treatment
  - acute: Valsalva or carotid massage, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina or CHF)
  - long-term: 1st line –  $\beta$ -blocker, diltiazem, digoxin; 2nd line – flecainide, propafenone; 3rd line – catheter ablation



The carotid massage is a constant pressure directed posteriorly against the carotid artery for 5-10 s. Always listen for bruits before palpation.

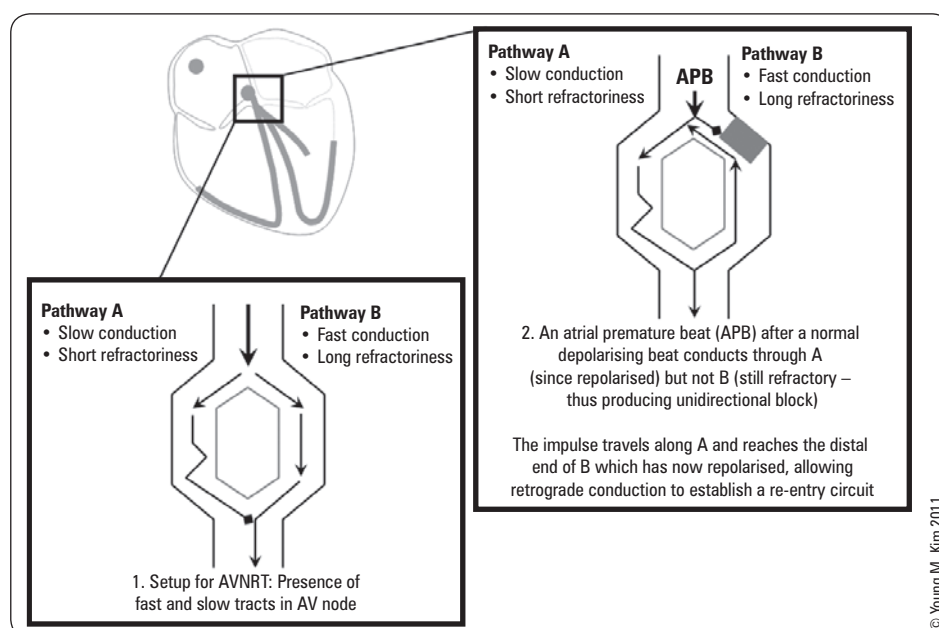


Figure 25. Mechanism for AVNRT

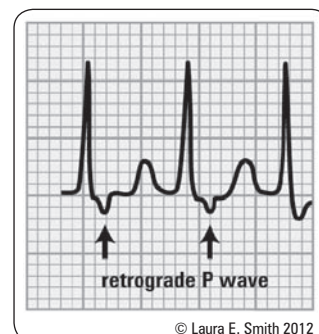


Figure 24. AVNRT

## Pre-Excitation Syndromes

- refers to a subset of SVTs mediated by an accessory pathway which can lead to ventricular pre-excitation

### Wolff-Parkinson-White (WPW) Syndrome

- congenital defect present in 1.5-2/1000 of the general population
- an accessory conduction tract (Bundle of Kent; can be in right or left atrium) abnormally allows early electrical activation of part of one ventricle
- impulses travel at a greater conduction velocity across the Bundle of Kent thereby effectively 'bypassing' AV node
- since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex – the so-called "delta wave"
- atrial impulses that conduct to the ventricles through both the Bundle of Kent and the normal AV node/His-Purkinje system generate a broad "fusion complex"
- ECG features of WPW
  - PR interval <120 msec
  - delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  - widening of the QRS complex due to premature activation
  - secondary ST segment and T wave changes
  - tachyarrhythmias may occur – most often AVRT and AFib

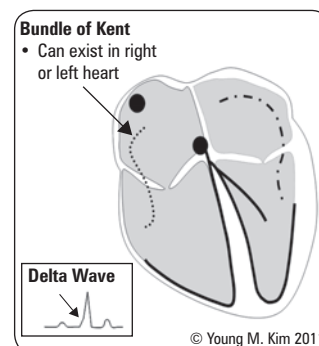


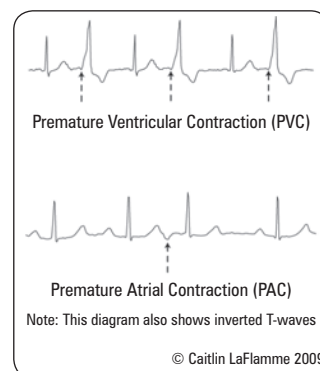
Figure 26. Accessory pathway conduction in WPW causes early ventricular activation leading to the appearance of a delta wave (slurred upstroke of the QRS) on the ECG before usual conduction occurs across the AV node

### AFib in WPW Patients

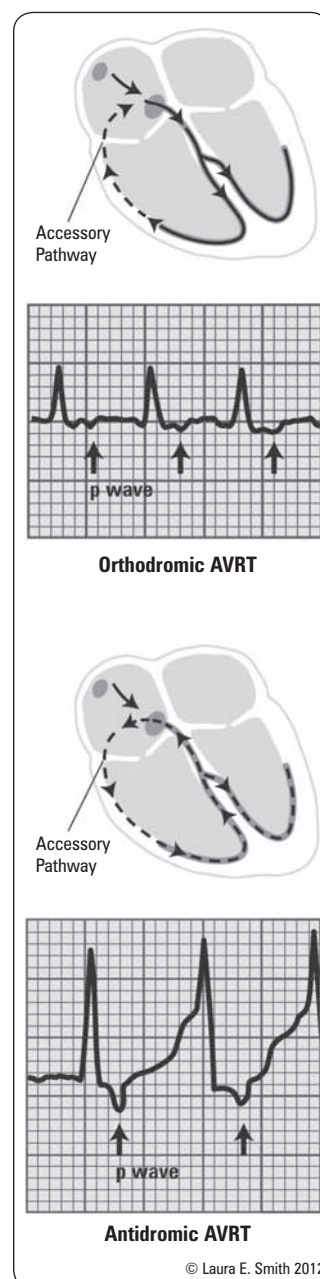
- AFib is the index arrhythmia in up to 20% of patients with WPW syndrome
  - it is usually intermittent rather than persistent or permanent
- rapid atrial depolarizations in AFib are conducted through the bypass tract which is not able to filter impulses like the AV node can
- consequently the ventricular rate becomes extremely rapid ( $>200$  bpm) and the QRS complex widens
- treatment: electrical cardioversion, IV procainamide or IV amiodarone
  - do not use drugs that slow AV node conduction (digoxin,  $\beta$ -blockers) as this may cause preferential conduction through the bypass tract and precipitate VF
  - long-term: ablation of bypass tract if possible

### AV Re-Entrant Tachycardia (AVRT)

- re-entrant loop via accessory pathway and normal conduction system
- initiated by a premature atrial or ventricular complex
- **orthodromic AVRT**: stimulus from a premature complex travels up the bypass tract (V to A) and down the AV node (A to V) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system) (see Figure 28)
  - comprises 95% of the reentrant tachycardias associated with WPW syndrome
- **antidromic AVRT**: more rarely the stimulus goes up the AV node (V to A) and down the bypass tract (A to V); wide and abnormal QRS as ventricular activation is only via the bypass tract
- treatment
  - acute: similar to AVNRT except avoid long-acting AV nodal blockers, e.g. digoxin and verapamil
  - long-term: for recurrent arrhythmias ablation of the bypass tract is recommended
    - ♦ drugs such as flecainide and procainamide can be used



**Figure 27. PVC (with bigeminy pattern) and PAC**



**Figure 28. Orthodromic vs. antidromic AVRT**

## Ventricular Tachyarrhythmias

### Premature Ventricular Contraction (PVC) or Ventricular Premature Beat (VPB)

- QRS width  $>120$  msec, no preceding P wave, bizarre QRS morphology
- origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
- PVCs may be benign but are usually significant in the following situations:
  - consecutive ( $\geq 3 =$  VT) or multiform (varied origin)
  - PVC falling on the T wave of the previous beat ("R on T phenomenon"): may precipitate ventricular tachycardia or VF

### Accelerated Idioventricular Rhythm

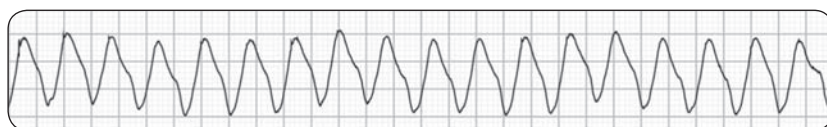
- ectopic ventricular rhythm with rate 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute MI or other types of heart disease (cardiomyopathy, hypertensive, valvular) but it does not affect prognosis and does not usually require treatment

### Ventricular Tachycardia (VT)

- 3 or more consecutive ectopic ventricular complexes (Figure 29)
  - rate  $>100$  bpm (usually 140-200)
  - ventricular flutter: if rate  $>200$  bpm and complexes resemble a sinusoidal pattern
  - "sustained VT" if it lasts longer than 30 s
  - ECG characteristics: wide regular QRS tachycardia (QRS usually  $>140$  msec); AV dissociation; bizarre QRS pattern. Also favour Dx of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
  - occasionally during VT supraventricular impulses may be conducted to the ventricles generating QRS complexes with normal or aberrant supraventricular morphology ("ventricular capture") or summation pattern ("fusion complexes")
- **monomorphic VT**
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - typically result from intraventricular re-entry circuit
  - potential causes: chronic infarct scarring, acute MI/ischemia, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances
- **polymorphic VT**
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm) vs. monomorphic VT
  - potential causes: acute MI, severe or silent ischemia, and predisposing factors for QT prolongation (see *Torsades de Pointes*, C20)



- treatment
  - sustained VT (>30 s) is an emergency, requiring immediate treatment
  - hemodynamic compromise: electrical cardioversion
  - no hemodynamic compromise: electrical cardioversion, lidocaine, amiodarone, type Ia agents (procainamide, quinidine)



**Figure 29. Ventricular tachycardia (monomorphic)**

**Table 4. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy\***

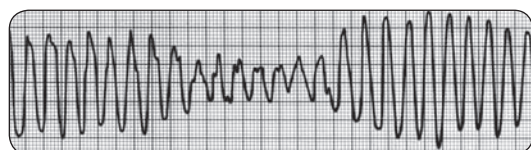
Clinical Clues		ECG Clues	
Presenting symptoms	Not helpful	AV dissociation	VT
History of CAD and previous MI	VT	Capture or fusion beats	VT
Physical exam		QRS width > 140 msec	VT
Cannon "a" waves Variable S1	VT	Extreme axis deviation (left or right superior axis)	VT
Carotid sinus massage/adenosine terminates arrhythmia	SVT**	Positive QRS concordance (R wave across chest leads)	VT
		Negative QRS concordance (S wave across chest leads)	May suggest VT
		Axis shift during arrhythmia	VT (polymorphic)

\*If patient > 65 and previous MI or structural heart disease, then chance of VT > 95%

\*\*May terminate VT in some patients with no structural heart disease

### Torsades de Pointes

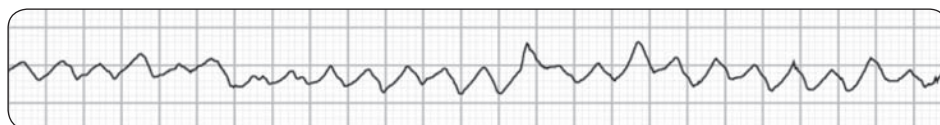
- a variant of polymorphic VT that occurs in patients with baseline QT prolongation – “twisting of the points” (Figure 30)
- looks like usual VT except that QRS complexes “rotate around the baseline” changing their axis and amplitude
- ventricular rate >100 bpm, usually 150-300 bpm
- etiology: predisposition in patients with prolonged QT intervals
  - congenital long QT syndromes
  - drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  - electrolyte disturbances: hypokalemia, hypomagnesemia
  - nutritional deficiencies causing above electrolyte abnormalities
- treatment: IV magnesium, temporary pacing, isoproterenol and correct underlying cause of prolonged QT, electrical cardioversion if hemodynamic compromise



**Figure 30. Torsades de pointes**

### Ventricular Fibrillation (VFib)

- chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology (Figure 31)
- terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and cardiac output, and electrical defibrillation is carried out
- most frequent cause of sudden death
- refer to ACLS algorithm for complete therapeutic guidelines



**Figure 31. Ventricular fibrillation**



#### Arrhythmias that May Present as a Wide QRS Tachycardia

- Ventricular tachycardia
- SVT with aberrant conduction (rate related)
- SVT with preexisting BBB or nonspecific intraventricular conduction defect
- AV conduction through a bypass tract in WPW patients during an atrial tachyarrhythmia (e.g. atrial flutter, atrial tachycardia)
- Antidromic AVRT in WPW patients (see Pre-excitation Syndromes, C18)

## Electrophysiology (EPS) Studies

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of SA node dysfunction and localize site of AV conduction block
- tachyarrhythmias: map for possible ablation or to assess inducibility of ventricular tachycardia

## Electrical Pacing

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia in the setting of heart disease

### Pacemaker Indications

- SA node dysfunction (most common): symptomatic bradycardia  $\pm$  hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

### Pacemaker Complications

- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism), pacemaker leads (perforation, malposition), pocket hematomas and infection
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure, pacemaker syndrome and pacemaker mediated tachycardia

### Pacing Techniques

- temporary: transvenous (jugular, subclavian, femoral) or external pacing
- permanent: transvenous into RA, apex of RV or both
- can sense and pace atrium, ventricle or both
- new generation: rate responsive, able to respond to physiologic demand
- biventricular

## Implantable Cardioverter Defibrillators (ICDs)

- sudden cardiac death (SCD) usually results from ventricular fibrillation (VFib), sometimes preceded by monomorphic or polymorphic ventricular tachycardia (VT)
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention
- benefit seen in patients with ischemic and non-ischemic cardiomyopathy, depressed left ventricular ejection fraction (LVEF), prolonged QRS
- see *Heart Failure*, C30 for current treatment recommendations

## Catheter Ablation

### Techniques

- radiofrequency (RF) energy: a low-voltage high-frequency form of electrical energy (similar to cautery). RF energy produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth

### Indications

- paroxysmal SVT
  - AVNRT: accounts for more than half of all cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
  - re-entrant rhythm, with an accessory AV connection as the retrograde limb
  - corrected by targeting the accessory pathway
- atrial flutter: flutter focus in RA
- AFib: potential role for pulmonary vein ablation
- ventricular tachycardia: focus arises from the right ventricular outflow tract and less commonly originates in the inferoseptal left ventricle near the apex (note: majority of cases of VT are due to scarring from previous MI and cannot be ablated)



### CCS Consensus Conference 2003: Assessment of the Cardiac Patient for Fitness to Drive and Fly – Executive Summary

*Can J Cardiol* 2004;20:1313-1323

In both primary and secondary prevention ICD patients with private driving licenses, no restrictions to drive directly following implantation or an inappropriate shock are warranted. However, following an appropriate shock these patients are at an increased risk to cause harm to other road users and therefore should be restricted to drive for a period of 2 and 4 mo, respectively. In addition, all ICD patients with commercial driving licenses have a substantial elevated risk to cause harm to other road users during the complete follow-up after both implantation and shock and should therefore be restricted to drive permanently.



### Systematic Review: Implantable Cardioverter Defibrillators for Adults with Left Ventricular Systolic Dysfunction

*Ann Intern Med* 2007;147:251-62

**Study:** Meta-review of 12 RCTs used for ICD efficacy, 5 RCTs and 48 observational studies for effectiveness, and 21 RCTs and 43 observational studies for safety review.

**Population:** 8516 patients for ICD efficacy, 26,840 patients for effectiveness, and 86,809 patients for safety review with left ventricular ejection fraction  $\leq 0.35$ .

**Intervention:** ICD implantation.

**Outcomes:** All-cause mortality and adverse events

**Results:** ICDs reduced all-cause mortality by 20% (95% CI, 10%-29%;  $I^2 = 44.4\%$ ) with greatest reduction (54%) in sudden cardiac death (CI, 37%-63%;  $I^2 = 0\%$ ). Observational studies had a reduced relative risk of 0.54 for all-cause mortality versus RCTs (CI 0.43-0.58,  $I^2 = 60.4\%$ ). Rates of success of ICD implantation were 99% (CI 98.8%-99.3%) with a 1.2% (CI 0.9%-1.5%) chance of peri-implantation death. Post-implantation complications (per 100 patient-yr) were: 1.4 (CI 1.2-1.6) device malfunctions; 1.5 (CI 1.3-1.8) lead problems; 0.6 (CI 0.5-0.8) implant site infection and 19.1 (CI 16.5-22.0) inappropriate discharges in RCTs versus a rate of 4.9 (CI 4.5-5.3) inappropriate discharges in observational studies.

**Conclusion:** ICDs are safe and effective in reducing mortality in adult patients with LV systolic dysfunction but carry significant risks of inappropriate discharges. Differences between RCTs and observational studies show that improved risk stratification of patients may further improve outcomes and reduce adverse events.

### Major Complications

- 1% of patients
- death: 0.1-0.2%
- cardiac: high grade AV block requiring permanent pacemaker, tamponade, pericarditis
- vascular: hematoma, vascular injury, thromboembolism, TIA/stroke
- pulmonary: PE

## Ischemic Heart Disease

### Epidemiology

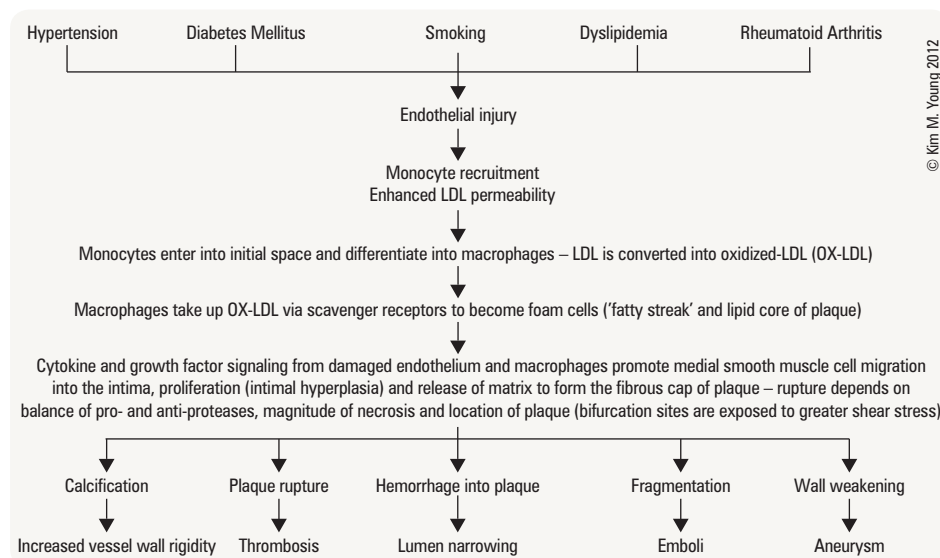
- most common cause of cardiovascular morbidity and mortality
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- male:female ratio = 2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease please see [Family Medicine](#), FM19



**Table 5. Risk Factors and Markers for Atherosclerotic Heart Disease**

Non-modifiable Risk Factors	Modifiable Risk Factors	Markers of Disease
Age	Hyperlipidemia*	Elevated lipoprotein(a)
Male, postmenopausal female	Hypertension (HTN)*	Hyperhomocysteinemia
Family history (FHx) of MI*	Diabetes mellitus (DM)*	Elevated high-sensitivity C-reactive protein (hsCRP)
First degree male relative <55	Cigarette smoking*	Coronary artery calcification
First degree female relative <65	Metabolic syndrome	
	Obesity	
	Sedentary lifestyle	
	Heavy alcohol intake	

\* Major risk factor



**Figure 32. Pathophysiology of atherosclerosis**

## Chronic Stable Angina

### Definition

- symptom complex resulting from an imbalance between oxygen supply and demand in the myocardium

### Etiology and Pathophysiology

- factors that decrease myocardial oxygen supply
  - decreased luminal diameter: atherosclerosis, vasospasm
  - decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - decreased hemoglobin: anemia
  - decreased SaO<sub>2</sub>: hypoxemia
  - congenital anomalies



Chronic stable angina is most often due to a fixed stenosis caused by an atheroma.

Acute coronary syndromes are the result of plaque rupture.

- factors that increase myocardial oxygen demand
  - increased heart rate: hyperthyroidism
  - increased contractility: hyperthyroidism
  - increased wall stress: myocardial hypertrophy, aortic stenosis

### Signs and Symptoms

- typical: retrosternal chest pain, tightness or discomfort radiating to left ( $\pm$  right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety
- predictably precipitated by the “3 Es”: exertion, emotion, eating
- brief duration, lasting <10-15 min and typically relieved by rest and nitrates
- Levine’s sign: clutching fist over sternum when describing chest pain
- anginal equivalents: dyspnea, acute LV failure, flash pulmonary edema

### Clinical Assessment

- history including directed risk factor assessment and physical exam
- labs: Hb, associated with diaphoresis, fasting glucose, fasting lipid profile
- ECG (at rest and during episode of chest pain if possible)
- CXR (suspected heart failure, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs or symptoms of pulmonary disease)
- stress testing (see *Cardiac Diagnostic Tests*, C5) or angiography
- echo
  - to assess systolic murmur suggestive of aortic stenosis, mitral regurgitation and/or HCM
  - to assess LV function in patients with Hx of prior MI, pathological Q waves, signs or symptoms of congestive heart failure (CHF)

### Differential Diagnosis

- see *Differential Diagnosis of Common Presentations*, C4

### Treatment of Chronic Stable Angina

#### 1. General measures

- goals: to reduce myocardial oxygen demand and/or increase oxygen supply
- lifestyle modification (diet, exercise)
- treatment of risk factors: statins (see [Endocrinology](#), E5, [Family Medicine](#), FM9 for target lipid guidelines), antihypertensives, etc.

#### 2. Antiplatelet therapy (first-line therapy)

- ASA
- clopidogrel when ASA absolutely contraindicated

#### 3. $\beta$ -blockers (first-line therapy – decrease overall mortality)

- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via  $\beta_2$  receptors)
- avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand

#### 4. Nitrates (symptomatic control, no clear impact on survival)

- decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
- maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)

#### 5. Calcium channel blockers (CCBs, second-line or combination)

- increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
- caution: verapamil/diltiazem combined with  $\beta$ -blockers may cause symptomatic sinus bradycardia or AV block

#### 6. ACE inhibitors (ACEI, not used to treat symptomatic angina)

- angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. hypertension, diabetes, proteinuric renal disease, previous MI with LV dysfunction)
- benefit in all patients at high risk for CV disease (concomitant DM, renal dysfunction or LV systolic dysfunction)
- angiotensin II receptor blockers (ARBs) can be used when ACEI contraindicated (e.g. hypersensitivity, angioedema)

#### 7. Invasive strategies

- revascularization (see *Coronary Revascularization*, C28 and *COURAGE trial* sidebar)

### VARIANT ANGINA (Prinzmetal’s Angina)

- myocardial ischemia secondary to coronary artery vasospasm, with or without atherosclerosis
- uncommonly associated with infarction or LV dysfunction
- typically occurs between midnight and 8 AM, unrelated to exercise, relieved by nitrates
- typically ST elevation on ECG
- diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
- treat with nitrates and CCBs

### SYNDROME X

- typical symptoms of angina but normal angiogram
- may show definite signs of ischemia with exercise testing
- thought to be due to inadequate vasodilator reserve of coronary resistance vessels
- better prognosis than overt epicardial atherosclerosis



#### Canadian Cardiovascular Society (CCS) Functional Classification of Angina

- **Class I:** ordinary physical activity (walking, climbing stairs) does not cause angina; angina with strenuous, rapid, or prolonged activity
- **Class II:** slight limitation of ordinary activity: angina brought on at >2 blocks on level or climbing >1 flight of stairs or by emotional stress
- **Class III:** marked limitation of ordinary activity: angina brought on at <2 blocks on level or climbing <1 flight of stairs
- **Class IV:** inability to carry out any physical activity without discomfort; angina may be present at rest



#### Optimal Medical Therapy with or without PCI for Stable Coronary Disease. COURAGE Trial

NEJM 2007;356:1503-16

**Study:** Randomized, controlled trial with median follow-up of 4.6 yr.

**Population:** 2287 patients who had objective evidence of myocardial ischemia and significant stable coronary artery disease.

**Intervention:** Patients were randomized to receive intensive pharmacologic therapy and lifestyle intervention with or without percutaneous coronary intervention (PCI).

**Outcome:** Primary outcome was all-cause mortality and nonfatal myocardial infarction (MI). Secondary outcome had additional events of stroke, all MI, and hospitalization for unstable angina with negative biomarkers.

**Results:** There was no significant difference in primary (unadjusted hazard ratio: 1.05;  $p=0.62$ ) or secondary outcomes (hazard ratio: 1.05;  $p=0.62$ ) between the PCI and non-PCI intervention groups. The PCI group had significantly lower rates of subsequent revascularization at 4.6 yr of follow-up (hazard ratio 0.60,  $p<0.001$ ) and was more angina-free in the first 4 yr of follow-up.

**Conclusions:** PCI as an adjunct in initial management in patients with significant stable coronary artery disease does not reduce mortality, MI, stroke or hospitalization for ACS, but does provide angina relief and reduced risk of revascularization.

## Acute Coronary Syndromes (ACS)

### Definition

- ACS includes the spectrum of UA, NSTEMI and STEMI. This distinction aids in providing the appropriate therapeutic intervention
  - MI is defined by evidence of myocardial necrosis. It is diagnosed by a rise/fall of serum markers plus any one of:
    - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
    - ECG changes (ST-T changes, new BBB or pathological Q waves)
    - imaging evidence (myocardial loss of viability, wall motion abnormality or intracoronary thrombus)
  - if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
  - NSTEMI meets criteria for myocardial infarction without ST elevation or BBB
  - STEMI meets criteria for myocardial infarction characterized by ST elevation or new BBB
- UA is clinically defined by any of the following:
  - accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion, decreased response to treatment
  - angina at rest
  - new-onset angina
  - angina post-MI or post-procedure (e.g. percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG])

### Investigations

- history and physical
  - note that up to 30% of MIs are unrecognized or “silent” due to atypical symptoms – more common in women, DM, elderly, post-heart transplant (because of denervation)
- ECG
- CXR
- labs
  - serum cardiac biomarkers for myocardial damage (repeat 8 h later) (see *Cardiac Biomarkers*, C9)
  - CBC, INR/PTT, electrolytes and magnesium, creatinine, urea, glucose, serum lipids
  - draw serum lipids within 24–48 h because values are unreliable from 2–48 d post-MI

## MANAGEMENT OF ACUTE CORONARY SYNDROMES

### 1. General measures

- ABCs: assess and correct hemodynamic status first
- bed rest, cardiac monitoring, oxygen
- nitroglycerin SL followed by IV
- morphine IV

### 2. Anti-platelet and anticoagulation therapy

- ASA 162–325 mg chewed
- NSTEMI
  - clopidogrel 300 mg loading dose, then 75 mg QD in addition to ASA or if ASA contraindicated, subcutaneous low molecular weight heparin or IV unfractionated heparin (UFH) (LMWH preferable, except in renal failure or if CABG is planned within 24 h)
- if PCI is planned: clopidogrel 300 mg loading dose and IV GP IIb/IIIa inhibitor (e.g. abciximab)
- anticoagulation options depend on reperfusion strategy:
  - primary PCI: UFH during procedure; bivalirudin is a possible alternative
  - thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
  - no reperfusion: LMWH (enoxaparin) until discharge from hospital
- continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)

### 3. $\beta$ -blockers

- first dose IV followed by oral administration
- STEMI: contraindications include signs of heart failure, low output states, risk of cardiogenic shock, heart block, asthma or airway disease; initiate orally within 24 h of diagnosis when indicated
- if  $\beta$ -blockers are contraindicated or if  $\beta$ -blockers/nitrates fail to relieve ischemia, non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (calcium channel blockers do not prevent MI or decrease mortality)



#### Is this Patient Having a Myocardial Infarction? From The Rational Clinical Examination

JAMA 2009; <http://www.jamaevidence.com/content/3484335>

**Study:** Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of an acute myocardial infarction.

**Results:** In patients with normal or non-diagnostic ECG, no established CAD, and prolonged or recurrent chest pain typical of their usual discomfort, radiation of pain to the shoulder OR both arms had the highest positive likelihood ratio (+LR) of 4.1 (95% CI, 2.5–6.5) and a negative likelihood ratio (–LR) of 0.68 (95% CI, 0.52–0.89). Radiation to right arm had a +LR of 3.8 (95% CI, 2.2–6.6) and –LR of 0.86 (95% CI, 0.77–0.96), vomiting had a +LR of 3.5 (95% CI, 2.0–6.2) and –LR of 0.87 (95% CI, 0.79–0.97), while radiation to left arm only had a +LR of 1.3 (95% CI, 0.93–1.8) and a –LR of 0.9 (95% CI, 0.76–1.1).

**Conclusions:** The most compelling features that increase likelihood of an MI are ST-segment and cardiac enzyme elevation, new Q-wave, and presence of an S3 heart sound. In patients where the diagnosis of MI is uncertain, radiation of pain to the shoulder OR both arms, radiation to the right arm, and vomiting had the best predictive values, while radiation to the left arm is relatively non-diagnostic.



#### TIMI Risk Score for UA/NSTEMI

Characteristics	Points
<b>Historical</b>	
Age $\geq 65$ yr	1
$\geq 3$ risk factors for CAD	1
Known CAD (stenosis $\geq 50\%$ )	1
Aspirin <sup>®</sup> use in past 7 d	1
<b>Presentation</b>	
Recent ( $\leq 24$ h) severe angina	1
ST-segment deviation $\geq 0.5$ mm	1
Increased cardiac markers	1

Risk Score = Total Points

If TIMI risk score  $\geq 3$ , consider early LMWH and angiography

TIMI = thrombolysis in myocardial infarction

UA = unstable angina

JAMA 2000;284:835–842



#### Treatment of NSTEMI

##### BEMOAN

$\beta$ -blocker  
Enoxaparin  
Morphine  
O<sub>2</sub>  
ASA  
Nitrates



#### 4. Invasive strategies and reperfusion options

- **UA/NSTEMI:** early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  - ♦ recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  - ♦ CHF or LV dysfunction
  - ♦ hemodynamic instability
  - ♦ high ( $\geq 3$ ) TIMI risk score (tool used to estimate mortality following an ACS)
  - ♦ sustained ventricular tachycardia
  - ♦ dynamic ECG changes
  - ♦ high-risk findings on non-invasive stress testing
  - ♦ PCI within the previous 6 mo
  - ♦ repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high risk features
  - ♦ note: thrombolysis is NOT administered for UA/NSTEMI
- **STEMI**
  - ♦ after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - ♦ goal is to re-perfuse artery: thrombolysis (“EMS-to-needle”) within 30 min or primary PCI (“EMS-to-balloon”) within 90 min (depending on capabilities of hospital and access to hospital with PCI facility)
  - ♦ thrombolysis
    - preferred if patient presents  $\leq 12$  h of symptom onset, and  $< 30$  min after presentation to hospital, has contraindications to PCI, or PCI cannot be administered within 90 min
  - ♦ PCI
    - early PCI ( $\leq 12$  h after symptom onset and  $< 90$  min after presentation) improves mortality vs. thrombolysis with fewer intra-cranial hemorrhages and recurrent MIs
    - primary PCI: without prior thrombolytic therapy – method of choice for reperfusion in experienced centres (*JAMA* 2004; 291:736-39)
    - rescue PCI: following failed thrombolytic therapy (diagnosed when following thrombolysis, ST segment elevation fails to resolve below half its initial magnitude and patient still having chest pain)



#### Enoxaparin versus Unfractionated Heparin with Fibrinolysis for ST-elevation Myocardial Infarction

*NEJM* 2006;354:1477-88

**Study:** Prospective multicenter RCT.

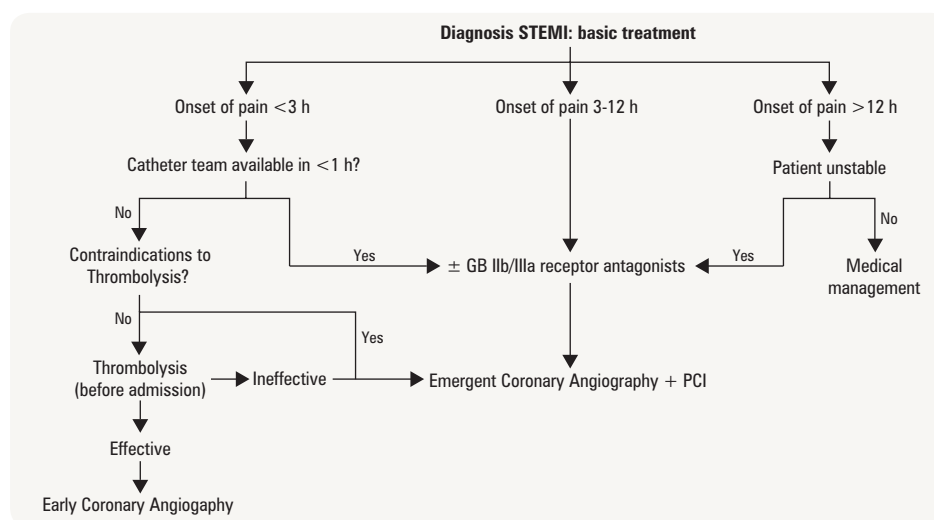
**Patients:** 20,479 patients (median age 60 yr, 77% male) with STEMI who were scheduled to undergo fibrinolysis.

**Intervention:** Patients were randomized to receive either enoxaparin or weight based unfractionated heparin in addition to thrombolysis and standard therapies.

**Primary Outcome:** Death or recurrent nonfatal MI 30 d post-event.

**Results:** The composite primary outcome occurred less often in the enoxaparin group compared with those who received unfractionated heparin (9.9% vs. 12.0%,  $p < 0.001$ , NNT=47). Taken separately, there was a trend toward reduced mortality (6.9% vs. 7.5%,  $p = 0.11$ ) and a significant reduction in nonfatal reinfarction (3.0% vs. 4.5%,  $p < 0.001$ ) in the enoxaparin group. The risk of major bleeding was significantly increased in the enoxaparin group (2.1% vs. 1.4%,  $p < 0.001$ , NNH=142).

**Conclusion:** In patients with STEMI receiving thrombolysis, enoxaparin is superior to unfractionated heparin in preventing recurrent nonfatal MI and may lead to a small reduction in mortality.



**Figure 33. Reperfusion strategy in STEMI**

**Table 6. Contraindications for Thrombolysis in STEMI**

Absolute	Relative
Prior intracranial hemorrhage	Chronic, severe, poorly controlled HTN
Known structural cerebral vascular lesion	Uncontrolled HTN (sBP > 180, dBP > 110)
Known malignant intracranial neoplasm	Current anticoagulation
Significant closed-head or facial trauma ( $\leq 3$ mo)	Noncompressible vascular punctures
Ischemic stroke ( $\leq 3$ mo)	Ischemic stroke ( $\geq 3$ mo)
Active bleeding	Recent internal bleeding ( $\leq 2-4$ wk)
Suspected aortic dissection	Prolonged CPR or major surgery ( $\leq 3$ wk)
	Pregnancy
	Active peptic ulcer disease



## Long-Term Management of ACS

- risk of progression to MI or recurrence of MI or death is highest within 1 mo
- at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- pre-discharge work-up: ECG and echo to assess residual LV systolic function
- drugs required in hospital to control ischemia should be continued after discharge in all patients
- other medications for long-term management of ACS are summarized below

### 1. General Measures

- education
- risk factor modification

### 2. Antiplatelet and Anticoagulation Therapy

- ECASA 75-162 mg daily
- clopidogrel 75 mg daily (at least 1 mo, up to 9-12 mo, if stent placed at least 12 mo)
- prasugrel 10 mg daily or ticagrelor 90 mg twice daily can be used as alternatives to clopidogrel when indicated
- $\pm$  warfarin x 3 mo if high risk (large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)

### 3. $\beta$ -Blockers (e.g. metoprolol 25-50 mg bid or atenolol 50-100 mg daily)

### 4. Nitrates

- alleviate ischemia but do not improve outcome
- use with caution in right-sided MI patients who have become preload dependent

### 5. Calcium Channel Blockers (NOT recommended as first line treatment, consider as alternative to $\beta$ -blockers)

### 6. Angiotensin-Converting Enzyme Inhibitors (ACEI)

- prevent adverse ventricular remodelling
- recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
- recommended for symptomatic CHF, reduced LVEF (<40%), anterior MI
- use ARBs in patients who are intolerant of ACEI

### 7. $\pm$ Aldosterone Antagonists

- if on ACEI and  $\beta$ -blockers and LVEF <40% and CHF or DM
- significant mortality benefit shown with eplerenone by 30 d

### 8. Statins (early, intensive, irrespective of cholesterol level; e.g. atorvastatin 80 mg daily)

### 9. Invasive Cardiac Catheterization if indicated (risk stratification, see Figure 34)

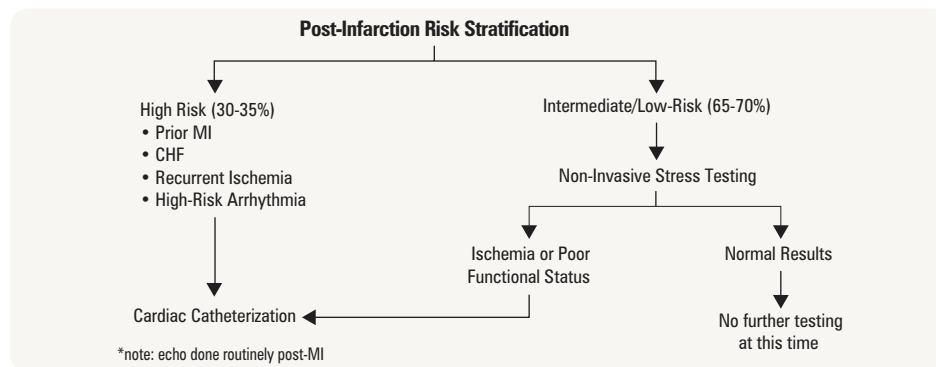


Figure 34. Post-MI risk stratification

## Prognosis following STEMI

- 5-15% of hospitalized patients will die
  - risk factors
    - ♦ infarct size/severity
    - ♦ age
    - ♦ co-morbid conditions
    - ♦ development of heart failure or hypotension
- post-discharge mortality rates
  - 6-8% within first year, half of these within first 3 months
  - 4% per year following first year
  - risk factors
    - ♦ LV dysfunction
    - ♦ residual myocardial ischemia
    - ♦ ventricular arrhythmias
    - ♦ history of prior MI



### Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

NEJM 2004;350:1495-1504

**Study:** Prospective, double blind, RCT; mean follow-up of 2 yr.

**Population:** 4,162 patients who had been hospitalized for an ACS within the preceding 10 d.

**Intervention:** Patients were randomized to receiving pravastatin 40 mg or atorvastatin 80 mg daily.

**Primary Outcome:** Composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 d after randomization), and stroke.

**Results:** High dose atorvastatin was associated with a 16% hazard ratio reduction ( $P=0.005$ ; 95% CI, 5-26%) in the primary outcome compared to standard dose pravastatin.

**Conclusions:** In patients whom recently experienced an ACS, high dose statin therapy provides greater protection against death and major cardiovascular events than standard dose therapy.



Resting LVEF is a useful prognostic factor.

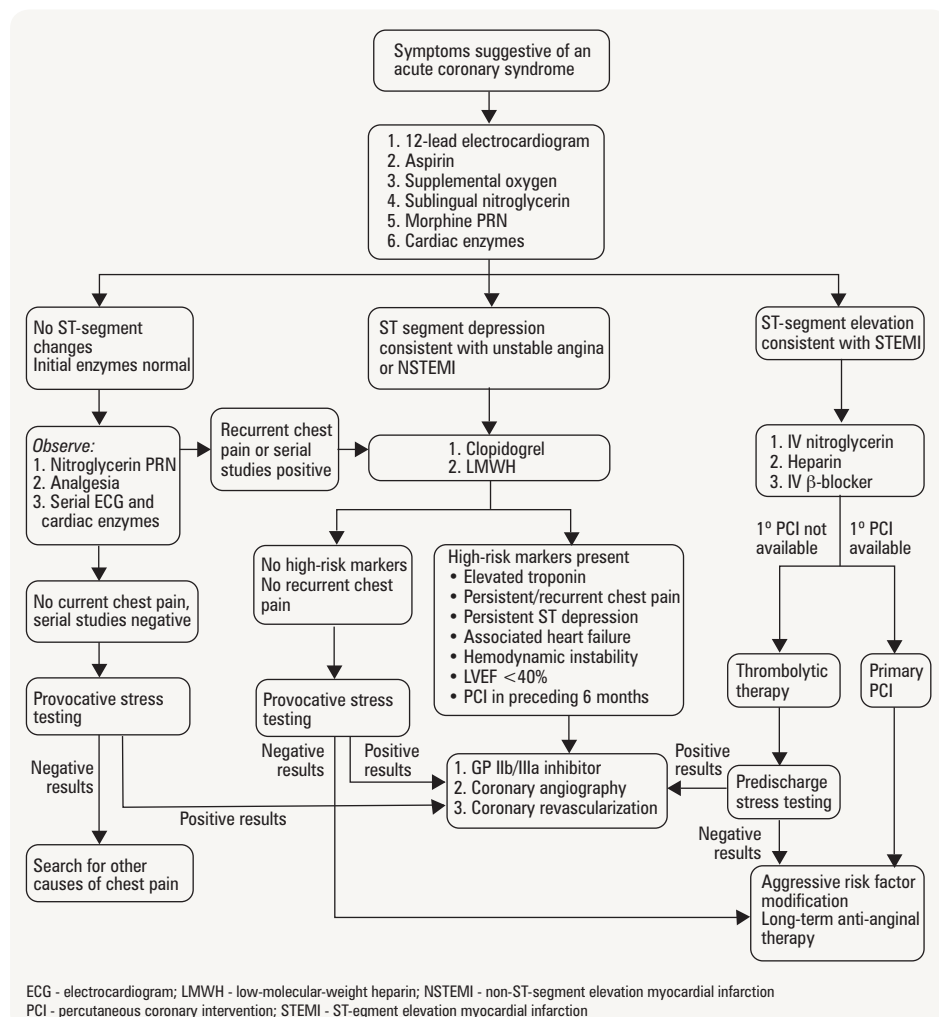
**Table 7. Complications of Myocardial Infarction**

Complication	Etiology	Presentation	Therapy
<b>Arrhythmia</b> 1. Tachycardia 2. Bradycardia	Sinus, AFib, VT, VFib Sinus, AV block	First 48 h First 48 h	See <i>Arrhythmias</i> , C12
<b>Myocardial Rupture</b> 1. LV free wall 2. Papillary muscle (→ MR) 3. Ventricular septum (→ VSD)	Transmural infarction Inferior infarction Septal infarction	1-7 d 1-7 d 1-7 d	Surgery Surgery Surgery
<b>Shock/CHF</b>	Infarction or aneurysm	Within 48 h	Inotropes, intra-aortic balloon pump
<b>Post-Infarct Angina</b>	Persistent coronary stenosis Multivessel disease	Anytime	Aggressive medical therapy PCI or CABG
<b>Recurrent MI</b>	Reocclusion	Anytime	Aggressive medical therapy PCI or CABG
<b>Thromboembolism</b>	Mural/apical thrombus DVT	7-10 d, up to 6 mo	Anticoagulation
<b>Pericarditis</b>	Inflammatory	1-7 d	ASA
<b>Dressler's syndrome</b>	Autoimmune	2-8 wk	

**Complications of MI****CRASH PAD**

Cardiac Rupture  
Arrhythmia  
Shock  
Hypertension/Heart failure  
Pericarditis/Pulmonary emboli  
Aneurysm  
DVT

## Treatment Algorithm for Chest Pain

**Figure 35. Treatment algorithm for chest pain**

Adapted from: Andreoli and Carpenter. Cecil Essentials of Medicine, 6th ed. Elsevier, 2004. p101. With permission from Elsevier

## Sudden Cardiac Arrest

### Definition

- unanticipated, non-traumatic cardiac death in a stable patient which occurs within 1 h of symptom onset; VFib is most common cause

### Etiology

- primary cardiac pathology
  - ischemia/MI
  - LV dysfunction
  - severe ventricular hypertrophy
    - ♦ HCM
    - ♦ AS
  - long QT syndrome
  - congenital heart disease
  - mutations in cardiac ion channels

### Management

- acute: resuscitate with prompt CPR and defibrillation
- investigate underlying cause (cardiac catheterization, electrophysiologic studies, echo)
- treat underlying cause
- antiarrhythmic drug therapy: amiodarone,  $\beta$ -blockers
- implantable cardioverter defibrillator (ICD)
- refer to ACLS guidelines (see [Anesthesia](#), A28)



## Coronary Revascularization

### PERCUTANEOUS CORONARY INTERVENTION (PCI)

- interventional cardiology technique aimed at relieving significant coronary stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

### Indications

- medically refractory angina
- NSTEMI/UA with high risk features (e.g. high TIMI risk score)
- primary/rescue PCI for STEMI

### Balloon Angioplasty and Intracoronary Stenting

- coronary lesions dilated with balloon inflation
- major complication is restenosis (approximately 15% at 6 mo), felt to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
  - bare metal stent (BMS)
  - drug-eluting stent (DES)
    - ♦ coated with antiproliferative drugs (sirolimus, paclitaxel)
    - ♦ reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
    - ♦ complication: late stent thrombosis (5 events per 1000 stents implanted)

### Adjunctive Therapies

- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
  - dual antiplatelet therapy (ASA and clopidogrel) for 1 mo with BMS or  $\geq 12$  mo with DES
  - ASA and prasugrel can be considered for those at increased risk of stent thrombosis

### Procedural Complications

- mortality and emergency bypass rates  $< 1\%$
- nonfatal MI: approximately 2-3%



#### Safety and Efficacy of Drug-Eluting and Bare Metal Stents

*Circulation* 2009;119:3198-3206

**Study:** Meta-analysis of RCTs and observational studies. 22 RCTs and 34 observational studies.

**Population:** 9,470 and 182,901 patients in RCTs and observational studies respectively who underwent percutaneous coronary intervention.

**Intervention:** Drug-Eluting Stents (DES) versus Bare Metal Stents (BMS).

**Outcome:** All-cause mortality, myocardial infarction (MI), and target vessel revascularization (TVR).

**Results:** No difference in mortality was found between DES vs. BMS by RCTs, while observational studies showed significantly lower mortality rates in DES-treated patients (hazard ratio (HR) 0.78,  $p < 0.001$ ). No difference in MI incidence was found in RCTs, while lower incidences of MI were found in observational studies (HR 0.87,  $p = 0.014$ ). DES has a significantly lower TVR rate in both RCT (HR 0.45,  $p < 0.001$ ) and observational studies (HR 0.46,  $p < 0.001$ ).

**Conclusions:** DES significantly reduces rates of TVR compared to BMS. Although there is no difference in mortality or MI incidence as found by RCTs, observational studies suggest lowered mortality and MI rates in patients with DES over BMS.

## CORONARY ARTERY BYPASS GRAFT (CABG) SURGERY

- objective of CABG is complete reperfusion of the myocardium

### Indications

- CABG
  - ≥50% diameter stenosis in the left main coronary artery
  - ≥70% diameter stenosis in three major coronary arteries
  - ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
  - survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery
- other:
  - ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
  - ≥70% diameter stenosis in the proximal LAD artery and evidence of extensive ischemia
  - multivessel CAD in patients with diabetes
  - LV systolic dysfunction (LVEF 35% to 50%) and significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization
- PCI
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG
- CABG or PCI
  - one or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

**Table 8. Choice of Revascularization Procedure**

	PCI	CABG
<b>Advantages</b>	Less invasive technique Decreased periprocedural morbidity and mortality Shorter periprocedural hospitalization	Greater ability to achieve complete revascularization Decreased need for repeated revascularization procedures
<b>Indications</b>	Single or double-vessel disease Inability to tolerate surgery	Triple-vessel or left main disease DM Plaque morphology unfavourable for PCI

**Table 9. Conduits for CABG**

Graft	Occlusion/Patency Rate	Considerations
<b>Saphenous Vein Grafts (SVG)</b>	At 10 yr, 50% occluded, 25% stenotic, 25% angiographically normal	Used when arterial grafts are not available or many grafts are required, such as triple or quadruple bypass
<b>Left Internal Thoracic/Mammary Artery (LITA/LIMA) (LIMA to LAD)</b>	90-95% patency at 15 yr	Most preferred option because of excellent patency Improved event-free survival (angina, MI) Decreased late cardiac events No increase in operative risk
<b>Right Internal Thoracic/Mammary Artery (RITA/RIMA)</b>	Pedicled RIMA patency comparable to LIMA Free RIMA patency less	Used in bilateral ITA/IMA grafting Patients receiving bilateral ITAs/IMAs have less risk of recurrent angina, late MI, angioplasty
<b>Radial Artery (free graft)</b>	85-90% patency at 5 yr	Prone to severe vasospasm postoperatively due to muscular wall
<b>Right Gastroepiploic Artery</b>	80-90% patency at 5 yr	Primarily used as an in situ graft to bypass the RCA Use limited because of the fragile quality of the artery, other technical issues, increased operative time (laparotomy incision) and incisional discomfort with associated ileus
<b>Complete Arterial Revascularization</b>		For younger patients (<60 yr of age) Is preferred due to longer term graft patency
<b>Redo Bypass Grafting</b>		Operative mortality 2-3 times higher than first operation 10% perioperative MI rate Reoperation undertaken only in symptomatic patients who have failed medical therapy and in whom angiography has documented progression of the disease Increased risk with redo-sternotomy secondary to adhesions which may result in laceration to aorta, RV, IMA/ITA and other bypass grafts

### Operative Issues

- left ventricular (LV) function is an important determinant of outcome of all heart diseases
- patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, PET scanning or MRI



**Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. SYNTAX Trial**  
*NEJM* 2009;360:961-972

**Study:** Prospective RCT.

**Population:** 1800 patients with untreated three-vessel or left main coronary artery disease and anatomically equivalent for both Percutaneous Intervention (PCI) and Coronary Artery Bypass Graft (CABG).

**Intervention:** PCI versus CABG.

**Outcome:** Composite of death from any cause, stroke, MI, or repeat revascularization in 12 mo post-intervention.

**Results:** Incidence of primary outcome was lower in the CABG intervention vs. PCI (12.4% vs. 17.8%,  $P=0.002$ , NNT=19). PCI was associated with significantly higher rates of repeat revascularization (13.5% vs. 5.9%,  $P<0.001$ ) and cardiac death (3.7% vs. 2.1%,  $P=0.05$ ), while CABG had higher rates of stroke (2.2% vs. 0.6%,  $P=0.03$ ).

**Conclusions:** In patients with three-vessel or left main coronary artery disease CABG is superior to PCI in preventing major adverse cardiovascular and cerebrovascular events within 12 mo of intervention.



**Effect of Perioperative Glucose-insulin-potassium Infusions on Mortality and Atrial Fibrillation After Coronary Artery Bypass Grafting: a Systematic Review and Meta-analysis**

*Can J Cardiol* 2010;26:178-184

Perioperative use of glucose-insulin-potassium or glucose-insulin infusions does not significantly reduce mortality or atrial fibrillation in patients undergoing CABG surgery. Unless future trial data in support of GIK/GI infusions become available, the routine use of these treatments in patients undergoing CABG surgery should be discouraged because the safety of these infusions has not been systematically examined.

**Table 10. Risk Factors for CABG Mortality and Morbidity (decreasing order of significance)**

Risk Factors for CABG Mortality	Risk Factors for CABG Postop Morbidity or Increased Length of Stay
Urgency of surgery (emergent or urgent)	Reoperation
Reoperation	Emergent procedure
Older age	Preoperative intra-aortic balloon pump (IABP)
Poor left ventricular function (see below)	Congestive heart failure
Female gender	CABG + valve surgery
Left main disease	Older age
Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, diabetes, cerebrovascular disease, and peripheral vascular disease	Renal dysfunction
	COPD
	DM
	Cerebrovascular disease

**Procedural Complications**

- CABG using cardiopulmonary bypass (CPB)
  - stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
  - immunosuppression
  - systemic inflammatory response leading to:
    - myocardial dysfunction
    - renal dysfunction
    - neurological injury
    - respiratory dysfunction
    - coagulopathies

**OFF-PUMP CORONARY ARTERY BYPASS (OPCAB) SURGERY****Procedure**

- OPCAB avoids the use of CPB by allowing surgeons to operate on a beating heart
  - stabilization devices (e.g. Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
  - procedure is safe and well tolerated by most patients; however, OPCAB surgery remains technically more demanding

**Indications**

- used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe peripheral vascular disease (PVD), severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g. Jehovah's Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- absolute contraindications:** hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels and calcified coronary vessels
- relative contraindications:** cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

**Outcomes**

- OPCAB decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
- no significant difference in terms of survival at 2 yr, frequency of cardiac events (MI, PCI, CHF, recurrent angina, redo CABG) or medication usage compared to on-pump CABG



**Does this Dyspneic Patient in the Emergency Department have Congestive Heart Failure?**  
JAMA 2005;294:1944-1956

	LR + (95% CI)	LR - (95% CI)
Initial clinical judgment	4.4 (1.8-10.0)	0.45 (0.28-0.73)
<b>Past Medical History</b>		
Heart failure	5.8 (4.1-8.0)	0.45 (0.38-0.53)
Myocardial infarction	3.1 (2.0-4.9)	0.69 (0.58-0.82)
Coronary artery disease	1.8 (1.1-2.8)	0.68 (0.48-0.96)
<b>Symptoms</b>		
Paroxysmal nocturnal dyspnea	2.6 (1.5-4.5)	0.7 (0.54-0.91)
Orthopnea	2.2 (1.2-3.9)	0.65 (0.45-0.92)
Dyspnea on exertion	1.3 (1.2-1.4)	0.48 (0.35-0.67)
<b>Physical Examination</b>		
Third heart sound	11 (4.9-25)	0.88 (0.83-0.94)
Jugular Venous distension	5.1 (3.2-7.9)	0.66 (0.57-0.77)
Rales	2.8 (1.9-4.1)	0.51 (0.37-0.70)
Lower extremity edema	2.3 (1.5-3.7)	0.64 (0.47-0.87)
<b>Chest Radiograph</b>		
Pulmonary venous congestion	12 (6.8-21)	0.48 (0.28-0.83)
Interstitial edema	12 (5.2-27)	0.68 (0.54-0.85)
Cardiomegaly	3.3 (2.4-4.7)	0.33 (0.23-0.48)
<b>ECG</b>		
Atrial fibrillation	3.8 (1.7-8.8)	0.79 (0.65-0.96)
Any abnormal finding	2.2 (1.6-3.1)	0.64 (0.47-0.88)

## Heart Failure

### Congestive Heart Failure (CHF)

**Definitions**

- heart failure: a complex clinical syndrome, resulting from almost any cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
- forward heart failure: heart unable to maintain adequate cardiac output to meet demand or is able to do so only by elevating filling pressure
- backward heart failure: heart unable to accommodate venous return resulting in elevated filling pressures and vascular congestion (systemic or pulmonary)
- heart failure can involve left side of heart (left heart failure), right side (right heart failure) or both (biventricular failure) (see Table 11)
- heart failure can also have components of ineffective ventricular filling (diastolic dysfunction) and/or contraction (systolic dysfunction)
- most cases associated with poor cardiac output (low-output heart failure); however, some cases of CHF not due to intrinsic cardiac disease but instead due to increased demand (high-output heart failure)

**Table 11. Signs and Symptoms of Left vs. Right Heart Failure**

	Left Failure	Right Failure
<b>Low cardiac output (forward)</b>	Fatigue Syncope Systemic hypotension Cool extremities Slow capillary refill Peripheral cyanosis Pulsus alternans Mitral regurgitation S3	Left failure symptoms if decreased RV output leads to LV underfilling Tricuspid regurgitation S3 (right-sided)
<b>Venous congestion (backward)</b>	Dyspnea, orthopnea, PND Cough Crackles	Peripheral edema Elevated JVP with abdominal jugular reflex and Kussmaul's sign Hepatomegaly Pulsatile liver

**Pathophysiology**

- primary insults (myocyte loss, overload) → pump dysfunction, which leads to:
  - remodeling (dilatation, hypertrophy)
  - neurohumoral activation → necrosis and apoptosis
- both pathways result in further damage (re-starting the cycle), edema, tachycardia, vasoconstriction, congestion
- compensatory response to myocardial stress (perpetuate disease process)
  - increased end-systolic ventricular pressure (pressure overload)
    - e.g. HTN, aortic stenosis → hypertrophy
  - increased end-diastolic ventricular volume (volume overload)
    - e.g. aortic regurgitation → cardiac dilatation
- systemic response to ineffective circulating volume
  - activation of sympathetic nervous and renin-angiotensin-aldosterone systems results in:
    - salt and water retention with intravascular expansion
    - increased heart rate and myocardial contractility
    - increased afterload

**Systolic Dysfunction**

- impaired myocardial contractile function → decreased LVEF and SV → decreased CO
- findings: apex beat displaced, S3, increased heart size on CXR, decreased LVEF, LV dilatation
- causes:
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - alcohol (and other toxins)
    - myocarditis
    - dilated cardiomyopathy (multiple causes – see *Dilated Cardiomyopathy*, C36)

**Heart Failure with Preserved Ejection Fraction (HFPEF)**

- previously known as “diastolic dysfunction”
- up to 1/2 of all HF patients have normal systolic function (i.e. normal ejection fraction) and the cause of heart failure is impaired diastolic filling; prevalence higher in older patients
- increased LV filling pressures produce venous congestion upstream (i.e. pulmonary and systemic venous congestion)
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal LVEF
- causes of decreased compliance:
  - transient: ischemia (relaxation of myocardium is active and requires ATP)
  - permanent
    - severe hypertrophy (HTN, aortic stenosis, HCM)
    - restrictive cardiomyopathy (e.g. amyloid)
    - MI

**High-Output Heart Failure**

- caused by demand for increased cardiac output
- often exacerbates existing heart failure or decompensates a patient with other cardiac pathology
- differential diagnosis: anemia, thiamine deficiency (beriberi), hyperthyroidism, A-V fistula or L-R shunting, Paget's disease, renal disease, hepatic disease

**Dichotomies of Heart Failure**

- Forward vs. Backward
- Left-sided vs. Right-sided
- Systolic vs. Diastolic dysfunction
- Low output vs. High output

**Use Ejection Fraction to Grade LV Dysfunction**

- Grade I (EF > 60%) (Normal)
- Grade II (EF = 40-59%)
- Grade III (EF = 21-39%)
- Grade IV (EF ≤ 20%)



**A Validated Clinical and Biochemical Score for the Diagnosis of Acute Heart Failure: the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Acute Heart Failure Score**  
*Am Heart J* 2006;151:48-54

Predictor	Possible Score
Age >75 yr	1
Orthopnea present	2
Lack of cough	1
Current loop diuretic use (before presentation)	1
Rales on lung exam	1
Lack of fever	2
Elevated NT-proBNP (>450 pg/mL if <50 yr, >900 pg/mL if >50 yr)	4
Interstitial edema on chest x-ray	2
Total	/14

Likelihood of heart failure:  
 Low = 0-5  
 Intermediate = 6-8  
 High = 9-14

Brain natriuretic peptide (BNP) is secreted by ventricles due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into ventricles, proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP. The above scoring algorithm developed by Baggish et al. is commonly used. A score of <6 has a negative predictive value of 98%, while scores ≥6 had a sensitivity of 96% and specificity of 84% (P<0.001) for the diagnosis of acute heart failure.

**New York Heart Association (NYHA) Functional Classification of Heart Failure**

- Class I:** ordinary physical activity does not cause symptoms of HF
- Class II:** comfortable at rest, ordinary physical activity results in symptoms
- Class III:** marked limitation of ordinary activity; less than ordinary physical activity results in symptoms
- Class IV:** inability to carry out any physical activity without discomfort; symptoms may be present at rest



## Etiologies of Primary Insults

- consider predisposing, precipitating and perpetuating factors

## Precipitants of Symptomatic Exacerbations

- consider natural progression of disease vs. new precipitant
- always search for reversible cause
- differential diagnosis can also be organized as follows:
  - new cardiac insult/disease: MI, arrhythmia, valvular disease
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection, etc.
  - failure to take medications as prescribed

## Investigations

- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), BUN, creatinine, fasting blood glucose, HbA1c, lipid profile, liver function tests, serum TSH,  $\pm$  ferritin, BNP, uric acid
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchiolar-alveolar cuffing
- echo: LVEF, cardiac dimensions, wall motion abnormalities, valvular disease, pericardial effusion
- radionuclide angiography: LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

## Acute Treatment of Pulmonary Edema

- treat acute precipitating factors (e.g. ischemia, arrhythmias)
- L** – Lasix® (furosemide) 40-500 mg IV
- M** – morphine 2-4 mg IV: decreases anxiety and preload (venodilation)
- N** – nitroglycerin: topical/IV/SL
- O** – oxygen: in hypoxemic patients
- P** – positive airway pressure (CPAP/BiPAP): decreases preload and need for ventilation when appropriate
- P** – position: sit patient up with legs hanging down unless patient is hypotensive
- in ICU setting or failure of LMNOPP, other interventions may be necessary
  - nitroprusside IV
  - hydralazine PO
  - sympathomimetics
    - dopamine
      - low dose: selective renal vasodilation (high potency D1 agonist)
      - medium dose: inotropic support (medium potency  $\beta$ 1 agonist)
      - high dose: increases SVR (low potency  $\beta$ 1 agonist), which is undesirable
    - dobutamine
      - selective inotrope ( $\beta$ 1 agonist) and arterial vasodilator ( $\beta$ 1 antagonist)
    - phosphodiesterase inhibitors (milrinone)
      - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
- consider pulmonary artery catheter to monitor pulmonary capillary wedge pressure (PCWP) if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
  - intra-aortic balloon pump (IABP)
  - left or right ventricular assist device (LVAD/RVAD)
  - cardiac transplant

## Long Term Management

- note that most evidence-based management applies to HFREF
- priorities in HFPEF focus on controlling systolic and diastolic hypertension, as a risk factor control measure

## Conservative Measures

- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease alcohol consumption, patient education, sodium and fluid restriction
- multidisciplinary heart failure clinics: for management of individuals at higher risk, or with recent hospitalization



### Five Most Common Causes of CHF

- CAD (60-70%)
- HTN
- Idiopathic (often dilated cardiomyopathy)
- Valvular (e.g. AS, AR and MR)
- Alcohol (dilated cardiomyopathy)



### Precipitants of Heart Failure

#### HEART FAILED

- Hypertension (common)
- Endocarditis/environment (e.g. heat wave)
- Anemia
- Rheumatic heart disease and other valvular disease
- Thyrotoxicosis
- Failure to take meds (very common)
- Arrhythmia (common)
- Infection/Ischemia/Infarction (common)
- Lung problems (PE, pneumonia, COPD)
- Endocrine (pheochromocytoma, hyperaldosteronism)
- Dietary indiscretions (common)



Various clinical guidelines, including the Acute Heart Failure Syndromes AHA 2010 Guidelines, and the 2012 Canadian Cardiovascular Society (CCS) Heart Failure Management Guidelines, indicate the current approach of acute heart failure exacerbation may be too homogenous. The CCS guidelines in particular offer several suggestions, including cautious use of oxygen in normoxic patients due to the possible risk of causing increased systemic resistance and reduced cardiac output, reserving the use of non-invasive ventilation for patients not responding to medical therapy, as well as preference for high dose rather than low dose diuretic therapy.



The most common cause of right heart failure is left heart failure.



### Measuring NT-pro BNP

BNP is secreted by ventricles due to LV stretch and wall tension. Cardiomyocytes secrete BNP precursor that is cleaved into proBNP. After secretion into ventricles proBNP is cleaved into the active C-terminal portion and the inactive NT-proBNP portion.

NT-proBNP levels (pg/mL)	
Age	HF very likely
<50	>450
50-75	>900
>75	>1800

Limitations: Age, body habitus, renal function, pulmonary embolism

## Pharmacological Therapy

### 1. Vasodilators

- ACEI: standard of care – slows progression of LV dysfunction and improves survival
  - all symptomatic patients functional class II-IV
  - all asymptomatic patients with LVEF <40%
  - post-MI
- angiotensin II receptor blockers (ARBs)
  - second-line to ACEI if not tolerated, or as adjunct to ACEI if  $\beta$ -blockers not tolerated – hydralazine and nitrates
  - second-line to ACEI, decrease in mortality not as great as with ACEI
  - may consider in acute renal failure until creatinine stabilizes

### 2. $\beta$ -blockers: slow progression and improve survival

- class I-III with LVEF <40%
- stable class IV patients
- note: should be used cautiously, titrate slowly because may initially worsen CHF**

### 3. Diuretics: symptom control, management of fluid overload

- furosemide (40-500 mg daily) for potent diuresis
- metolazone may be used with furosemide to increase diuresis
- furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by  $\beta$ -blockers, ACEI, ARBs, and aldosterone antagonists

### 4. Aldosterone antagonists: mortality benefit in severe CHF

- spironolactone for class IIb and IV CHF already on ACEI and loop diuretic
- eplerenone may be considered if intolerable endocrine side effects
- note: potential for life threatening hyperkalemia
  - monitor  $K^+$  after initiation and avoid if  $Cr > 220 \mu\text{mol/L}$  or  $K^+ > 5.2 \text{ mmol/L}$

### 5. Inotropes: digoxin improves symptoms and decreases hospitalizations, no effect on mortality

- indications: patient in sinus rhythm and symptomatic on ACEI, or CHF and AFib
- patients on digitalis glycosides may worsen if these are withdrawn

### 6. Antiarrhythmic drugs: for use in CHF with arrhythmia

- can use amiodarone,  $\beta$ -blocker, or digoxin

### 7. Anticoagulants: warfarin for prevention of thromboembolic events

- prior thromboembolic event or AFib, presence of LV thrombus on echo
- possible benefit in other patients with LVEF <30% (controversial)

## Procedural Interventions

- resynchronization therapy: symptomatic improvement with biventricular pacemaker
  - consider if QRS >130 msec, LVEF <35%, and severe symptoms despite optimal therapy
  - greatest benefit likely with marked LV enlargement, mitral regurgitation, QRS >150 msec, high diuretic requirement
- ICD: mortality benefit in 1° prevention of sudden cardiac death
  - prior MI, optimal medical therapy, LVEF <30%, clinically stable
  - prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
- LVAD/RVAD (see *Ventricular Assist Devices*, C34)
- cardiac transplantation (see *Cardiac Transplantation*, C34)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see *Valvular Heart Disease*, C38)



### Features of Heart Failure on CXR

#### HERB-B

- Heart enlargement (cardiothoracic ratio >0.50)
- Pleural Effusion
- Re-distribution (alveolar edema)
- Kerley B lines
- Bronchiolar-alveolar cuffing



Patients on  $\beta$ -blocker therapy who have acute decompensated heart failure should continue  $\beta$ -blockers where possible (provided they are not in cardiogenic shock or in severe pulmonary edema).



### Can the Clinical Examination Diagnose Left-Sided Heart Failure in Adults?

#### From The Rational Clinical Examination

JAMA 2009; <http://www.jamaevidence.com/content/3478992>

**Study:** Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of congestive heart failure.

**Results:** The diagnosis of left ventricular dysfunction in patient after an MI based on the presence of radiographic pulmonary venous congestion with edema, rales one-third up the lung fields in the absence of a chronic pulmonary disease, or a 3rd heart sound had a positive likelihood ratio (+LR) of 3.1 (95% CI, 1.7-5.8) and a negative likelihood ratio (-LR) of 0.62 (95% CI, 0.46-0.83). In inpatients the combination of clinical findings, ECG and CXR had a +LR of 2.0 (95% CI, 1.6-2.5) and a -LR of 0.41 (95% CI, 0.30-0.56). Female sex [+LR, 1.6 (95% CI, 1.2-2.2)] and sBP  $\geq 160 \text{ mmHg}$  [+LR, 1.8 (95% CI, 1.3-2.6)] were most indicative for diastolic dysfunction. Heart rate  $\geq 100/\text{min}$  [+LR 0.43 (95% CI, 0.28-0.65)] and left atrial ECG abnormality [+LR 0.42 (95% CI, 0.26-0.63)] were most indicative for systolic dysfunction.

**Conclusions:** Patients with signs, symptoms and risk factors for systolic dysfunction should receive an ECG and CXR. Female sex and sBP  $\geq 160 \text{ mmHg}$  are suggestive of diastolic dysfunction; heart rate  $\geq 100/\text{min}$  and left atrial ECG abnormality suggest systolic dysfunction.



### Chronic Treatment of CHF

- ACE inhibitors\*
- $\beta$ -blockers\*
- $\pm$  Aldosterone antagonists\* (if severe CHF)
- Diuretic
- $\pm$  Inotrope
- $\pm$  Antiarrhythmic
- $\pm$  Anticoagulant

\*Mortality benefit

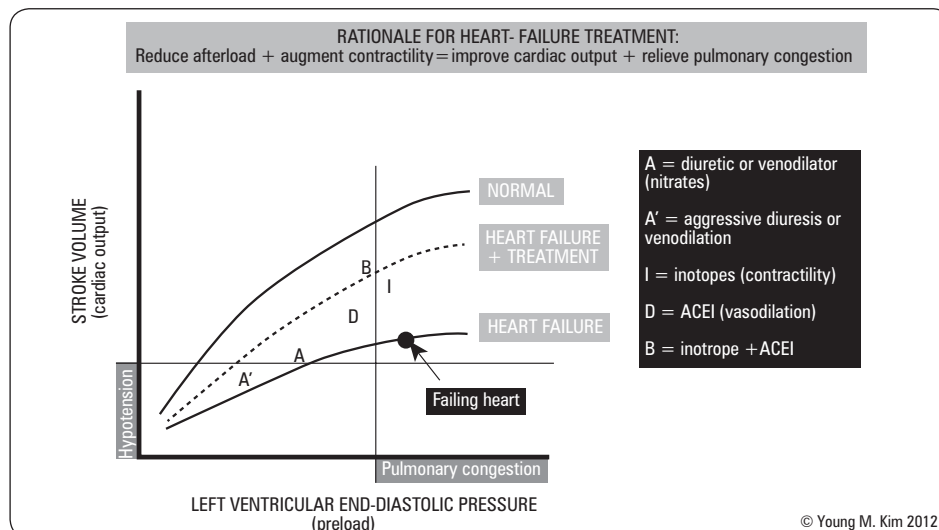


Figure 36. Effect of heart failure treatment on the Frank-Starling curve

## Sleep-Disordered Breathing

- 45-55% of patients with CHF have sleep disturbances, including Cheyne-Stokes breathing and sleep apnea (central or obstructive)
- associated with a worse prognosis and greater LV dysfunction
- nasal continuous positive airway pressure (CPAP) is effective in treating Cheyne-Stokes respiration/sleep apnea with improvement in cardiac function and symptoms

## Cardiac Transplantation

- treatment for end-stage heart disease; due to ischemic or non-ischemic cardiomyopathy
- worldwide 1-yr survival is 85-90%, 5-yr survival about 60%, annual mortality rate of 4%
- matching is according to blood type, body size and weight (should be within 25%), and HLA tissue matching (if time allows)

### Indications for Surgery

- severe cardiac disability despite maximal medical therapy (recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption  $<14$  mL/kg/min in absence of  $\beta$ -blocker)
- symptomatic cardiac ischemia refractory to conventional treatment (unstable angina not amenable to CABG or angioplasty with LVEF  $<30\%$ ; recurrent, symptomatic ventricular arrhythmias)
- exclusion of all surgical alternatives to cardiac transplantation

### Prerequisites

- emotionally stable with social support
- medically compliant and motivated
- relative contraindications: incurable malignancy, major systemic illness, irreversible major organ disease (e.g. renal, hepatic), active systemic infection (e.g. Hep C, HIV), obesity, irreversible pulmonary HTN (pulmonary vascular resistance [PVR]  $>6$  Wood units), severe COPD ( $FEV_1 <1$  L) or active drug addiction or alcoholism
- typically age  $<70$  yr

### Complications

- rejection
  - common, less than 5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
    - ♦ no noninvasive tests to detect rejection
  - risk of acute rejection is greatest during the first 3 mo after transplant
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
  - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft CAD
  - approximately 50% develop graft CAD within 5 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
  - second most common cause of late death following transplantation
  - cutaneous neoplasms most common, followed by non-Hodgkin's lymphoma and lung cancer
- immunosuppressive medication side effects (prednisone, cyclosporine, tacrolimus, sirolimus)

## Ventricular Assist Devices (VADs)

- work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD), or both ventricles (BiVAD)
- indications
  - bridge to transplantation
  - postoperative mechanical support when unable to separate from cardiopulmonary bypass despite inotropic and intra-aortic balloon pump (IABP) support
    - ♦ IABP is a catheter based device inserted into the aorta via the femoral artery that decreases myocardial  $O_2$  demand and increases blood flow to coronary arteries
  - postoperative cardiogenic shock



### Influence of Ejection Fraction on Cardiovascular Outcomes in a Broad Spectrum of Heart Failure Patients

*Circulation* 2005;112:3738-3744

**Purpose:** Understand the relationship between ejection fractions and cardiovascular risk in patients with heart failure.

**Methods:** 7599 patients from the CHARM study (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity; RCT comparing placebo vs. candesartan in patients with NYHA class II to IV). Compared LVEF to cardiovascular outcomes and causes of death.

**Results:** All-cause mortality increased by 39% per 10% reduction in LVEF below 45% (Hazard ratio 1.39, 95%CI 1.32-1.46). For LVEF  $>45\%$ , ejection fraction does not further contribute to assessment of cardiovascular risk in HF patients.

**Conclusions:** At LVEF  $<45\%$ , lower ejection fractions were associated with poorer cardiovascular outcomes.

LVEF	CHF Hospitalization	All-Cause Mortality
$\leq 22\%$	14.9%	15.4%
23-32%	10.9%	10.8%
33-42%	7.2%	7.4%
43-52%	5.7%	5.2%
$>52\%$	6.9%	5.7%



### Higher New York Heart Association Classes and Increased Mortality and Hospitalization in Patients with Heart Failure and Preserved Left Ventricular Function

*Am Heart J* 2006;151:444-450

**Purpose:** To establish the association between NYHA class and outcomes with heart failure and preserved systolic function

**Methods:** Retrospective follow-up study (median 38.5 mo) of 988 patients with heart failure with ejection fraction  $>45\%$ . Estimated risks of various outcomes using Cox proportional hazard models.

**Results:** Adjusted hazard ratio for all-cause mortality for NYHA class I, II, IV patients was 1.54, 2.56, and 8.46, respectively. Adjusted hazard ratio for all-cause hospitalization for NYHA class II, III, IV patients was 1.23, 1.71, and 3.4, respectively.

**Conclusions:** Higher NYHA classes were associated with poorer outcomes in patients with heart failure and preserved systolic function.

Proportions of NYHA I, II, III, and IV patients who died of all causes during the study were 14.3%.

NYHA	Proportion of All-Cause Hospitalization	Proportion of All-Cause Mortality
I	60.7%	14.3%
II	65.2%	21.3%
III	77.7%	35.9%
IV	75.0%	58.3%



### Effects of Donor Pre-treatment with Dopamine on Survival After Heart Transplantation: a Cohort Study of Heart Transplant Recipients Nested in a Randomized Controlled Multicenter Trial

*J Am Coll Cardiol* 2010;58:1768-1777

Treatment of brain-dead donors with dopamine of 4  $\mu$ g/kg/min will not harm cardiac allografts but appears to improve the clinical course of the heart allograft recipient.

## Myocardial Disease

### Definition of Cardiomyopathy

- intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
- functional classification: dilated, hypertrophic, or restrictive
- LV dysfunction 2° to MI often termed “ischemic cardiomyopathy”, is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD

**Table 12. Summary Table for CHF and Myocardial Disease**

SYSTOLIC HEART FAILURE		DIASTOLIC HEART FAILURE		
Dilated Cardiomyopathy	Secondary Causes	Hypertrophic Cardiomyopathy	Restrictive Cardiomyopathy	Secondary Causes
Idiopathic, infectious (e.g. myocarditis), alcohol, familial, collagen vascular disease, etc.	CAD, MI, DM, valvular (e.g. AR, MR)	Genetic disorder affecting cardiac sarcomeres (most common cause of sudden cardiac death in young athletes)	Amyloidosis, sarcoidosis, scleroderma, hemochromatosis, Fabry's, Pompe's Disease, Loeffler's, etc.	HTN, DM, valvular (e.g. AS), post-MI, transiently by ischemia, etc.



Canadian Cardiovascular Society Focused Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive: Fitness Following Left Ventricular Assist Device Implantation

*Can J Cardiol* 2012;28:137-140

Patients with a continuous flow, NYHA class I-III, LVAD that are stable 2 mo post LVAD implantation qualify for private driving only and are disqualified from commercial driving.



#### REMATCH Trial

*NEJM* 2001;345:1435-1443

Increased survival of 23% vs. 8% with LVAD vs. medical management of heart failure after 2 yr. Heartmate VAD has a biologic surface therefore does not require long-term anticoagulation but higher risk of infection.



#### Cardiomyopathy

##### HARD

Hypertrophic cardiomyopathy  
Arrhythmogenic right ventricular cardiomyopathy  
Restrictive cardiomyopathy  
Dilated cardiomyopathy

## Myocarditis

### Definition

- inflammatory process involving the myocardium ranging from acute to chronic; an important cause of dilated cardiomyopathy

### Etiology

- idiopathic
- infectious
  - viral (most common): coxsackie B, echovirus, poliovirus, HIV, mumps
  - bacterial: *S. aureus*, *C. perfringens*, *C. diphtheriae*, *Mycoplasma*, *Rickettsia*
  - fungi
  - spirochetal (Lyme disease – *Borrelia burgdorferi*)
  - Chagas disease (*Trypanosoma cruzi*), toxoplasmosis
- toxic: catecholamines, chemotherapy, cocaine
- hypersensitivity/eosinophilic: drugs (antibiotics, diuretics, lithium, clozapine), insect/snake bites
- systemic diseases: collagen vascular diseases (SLE, RA, others), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

### Signs and Symptoms

- constitutional symptoms
- acute CHF
- chest pain – due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- sudden death

### Investigations

- ECG: non-specific ST-T changes ± conduction defects
- bloodwork
  - increased CK, troponin, LDH, and AST with acute myocardial necrosis ± increased WBC, ESR, ANA, rheumatoid factor, complement levels
  - blood culture, viral titres and cold agglutinins for *Mycoplasma*
- CXR: enlarged cardiac silhouette
- echo: dilated, hypokinetic chambers, segmental wall motion abnormalities
- myocardial biopsy

### Management

- supportive care
- restrict physical activity
- treat CHF
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible

### Prognosis

- usually self-limited and often unrecognized, many recover
- sudden death in young adults
- may progress to dilated cardiomyopathy

## Dilated Cardiomyopathy (DCM)

### Definition

- unexplained dilation and impaired systolic function of one or both ventricles

### Etiology

- idiopathic (presumed viral or idiopathic) ~50% of DCM
- alcohol
- familial/genetic
- uncontrolled tachycardia (e.g. persistent rapid AFib)
- collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
- infectious: viral (coxsackie B, HIV), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), antiretrovirals, chloroquine, clozapine, TCA
- radiation

### Signs and Symptoms

- may present as:
  - CHF
  - systemic or pulmonary emboli
  - arrhythmias
  - sudden death (major cause of mortality due to fatal arrhythmia)

### Investigations

- bloodwork: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, TIBC
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (non-sustained VT)
- CXR: global cardiomegaly (globular heart), signs of CHF, pleural effusion
- echo: chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- coronary angiography: in selected patients to exclude ischemic heart disease

### Management

- treat underlying disease: e.g. abstinence from alcohol
- treat CHF: see *Heart Failure*, C30
- thromboembolism prophylaxis: anticoagulation with warfarin
  - indicated for: AFib, history of thromboembolism or documented thrombus
  - LVEF <30% (controversial)
- treat symptomatic or serious arrhythmias
- immunize against influenza and *S. pneumoniae*
- consider surgical options (e.g. LVAD, transplant, volume reduction surgery) in appropriate candidates with severe, drug refractory disease
- consider ICD among patients with a LVEF <30%

### Prognosis

- depends on etiology
- better with reversible underlying cause, worst with infiltrative diseases, HIV, drug-induced
- cause of death usually CHF (due to pump failure) or sudden death 2° to ventricular arrhythmias
- systemic emboli are significant source of morbidity
- 20% mortality in 1st yr, 10% per year after



**Major Risks Factors for DCM**  
Alcohol, cocaine, family history



**Abnormal Labs in DCM**

- High BNP
- High Cr
- High LFTs
- Low bicarbonate
- Low Na<sup>+</sup>

## Hypertrophic Cardiomyopathy (HCM)

- see 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy for details

### Definition

- defined as unexplained ventricular hypertrophy
- various patterns of HCM are classified, but most causes involve pattern of septal hypertrophy

### Etiology and Pathophysiology

- histopathologic features include myocyte disarray, myocyte hypertrophy, and interstitial fibrosis
- cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins (>400 mutations associated with autosomal dominant inheritance, incomplete penetrance)
- prevalence of 1/500-1/1000 in general population
- generally presents in early adulthood



**Hemodynamic Classification**

- hypertrophic obstructive cardiomyopathy (HOCM): dynamic LV outflow tract (LVOT) obstruction, either at rest or with provocation, defined as LVOT gradient of at least 30 mmHg
- non-obstructive HCM: no LVOT obstruction
- many patients have diastolic dysfunction (impaired ventricular filling secondary to LV hypertrophy which decreases compliance)

**Signs and Symptoms**

- clinical manifestations: asymptomatic (common, therefore screening is important), SOB on exertion, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
- pulses: rapid upstroke, “spike and dome” pattern in carotid pulse (in HCM with outflow tract obstruction)
- precordial palpation: PMI localized, sustained, double impulse, ‘triple ripple’ (triple apical impulse in HOCM), LV lift
- precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLSB or apex, enhanced by squat or Valsalva (murmur secondary to LVOT obstruction as compared to AS); often with pansystolic murmur due to mitral regurgitation

**Investigations**

- ECG/Holter monitor: LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- transthoracic echocardiography and echo-Doppler study: asymmetric septal hypertrophy (less commonly apical), systolic anterior motion (SAM) of mitral valve and MR; LVOT gradient can be estimated by Doppler measurement
- genetic cardiac resonance magnetic resonance imaging indicated when echocardiography is inconclusive for diagnosis
- cardiac catheterization (only when patient being considered for invasive therapy)

**Management**

- avoid factors which increase obstruction (e.g. volume depletion)
  - avoidance of all competitive sports
- treatment of obstructive HCM
  - medical agents:  $\beta$ -blockers, verapamil, phenylephrine, disopyramide
  - avoid nitrates, diuretics and ACEI as they increase LVOT gradient and worsen symptoms
- patients with drug-refractory symptoms
  - surgical myectomy
  - ICD placement
  - septal ethanol ablation
  - dual chamber pacing (rarely done)
- treatment of ventricular arrhythmias: amiodarone or ICD
- first-degree relatives of patients with HCM should be screened annually during adolescence (physical, ECG, 2D echo), then serially every 5 yr during adulthood
- first-degree genetic testing and family screening
- screening for sudden cardiac death: VF, VT, family history, unexplained syncope, maximal LV wall thickness  $\geq 30$  mm

**Prognosis**

- potential complications: AFib, VT, CHF, sudden cardiac death (1% risk/yr; most common cause of SCD in young athletes)
  - major risk factors for sudden death (consider ICD placement)
  - history of survived cardiac arrest/sustained VT
  - family history of multiple premature sudden deaths
  - other factors associated with increased risk of sudden cardiac death
    - ♦ syncope (presumed to be arrhythmic in origin)
    - ♦ non-sustained VT on ambulatory monitoring
    - ♦ marked ventricular hypertrophy (maximum wall thickness  $\geq 30$  mm)
    - ♦ abnormal BP in response to exercise (in patients  $< 40$  yr old with HCM)

## Restrictive Cardiomyopathy (RCM)

**Definition**

- impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)

**Etiology**

- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis
- storage diseases: hemochromatosis, Fabry's disease, Gaucher's disease, glycogen storage diseases
- endomyocardial
  - endomyocardial fibrosis, Loeffler's endocarditis or eosinophilic endomyocardial disease
  - radiation heart disease
  - carcinoid syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)



**RCM vs. Constrictive Pericarditis (CP)**  
Present similarly but CP is treatable with surgery.



### Clinical Manifestations

- CHF (usually with preserved LV systolic function), arrhythmias
- elevated JVP with prominent x and y descents, Kussmaul's sign
- S3, S4, MR, TR
- thromboembolic events

### Investigations

- ECG: low voltage, non-specific, diffuse ST-T wave changes  $\pm$  non-ischemic Q waves
- CXR: mild cardiac enlargement
- echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
- cardiac catheterization: increased end-diastolic ventricular pressures
- endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

### Management

- exclude constrictive pericarditis
- treat underlying disease: control HR, anticoagulate if AFib
- supportive care and treatment for CHF, arrhythmias
- heart transplant: might be considered for CHF refractory to medical therapy

### Prognosis

- depends on etiology



#### Key Investigations

- Echo: may show respiratory variation in blood flow in CP
- CT: may show very thickened pericardium and calcification in CP
- MRI: best modality to directly visualize pericardium and myocardium

## Valvular Heart Disease

- see *Guidelines on the Management of Valvular Heart Disease. Eur Heart J 2012;33(19):2451-2496* for details

### Infective Endocarditis (IE)

- see [Infectious Diseases](#), ID17
- American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  - only for patients with:
    - ♦ prosthetic valve material
    - ♦ past history of IE
    - ♦ certain types of congenital heart disease
    - ♦ cardiac transplant recipients who develop valvulopathy
  - only for the following procedures:
    - ♦ dental
    - ♦ respiratory tract
    - ♦ procedures on infected skin/skin structures/MSK structures
    - ♦ not GI/GU procedures specifically



### Rheumatic Fever

- see [Pediatrics](#), P61

### Prognosis

- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease – fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE  $\pm$  thromboembolism
- onset of symptoms usually after 10-20-yr latency from acute carditis of rheumatic fever
- mitral valve most commonly affected



#### A Bedside Clinical Prediction Rule for Detecting Moderate or Severe Aortic Stenosis

*J Gen Intern Med 1998;13:699-704*

**Study Design:** Blinded cross sectional study with 124 patients of an ambulatory cardiology clinic. Patients were examined for: 1) murmur over the right clavicle 2) murmur loudest at second right intercostal space 3) reduced intensity of S2 4) reduced volume of the carotid pulse 5) delayed carotid upstroke.

**Methods:** Patients were examined by blinded investigators and the clinical examination findings were compared to findings on subsequent echocardiography. Moderate to severe aortic stenosis was defined as a valve area  $<1.2$  cm<sup>2</sup> or a peak intensity gradient of  $>25$  mmHg.

**Results:** Absence of a murmur over the right clavicle ruled out aortic stenosis while presence of  $\geq 3$  of the 4 associated symptoms ruled in aortic stenosis (LR=40).

**Conclusions:** Bedside techniques can accurately rule in and rule out moderate to severe aortic stenosis.

### Choice of Valve Prosthesis

**Table 13. Mechanical Valve vs. Bioprosthetic Valve**

Mechanical Valve	Bioprosthetic Valve
Good durability	Limited long-term durability (mitral<aortic)
Less preferred in small aortic root sizes	Good flow in small aortic root sizes
Increased risk of thromboembolism (1-3%/yr); requires long-term anticoagulation with coumadin	Decreased risk of thromboembolism: long-term anticoagulation not needed for aortic valves
Target INR Aortic valves: 2.0-3.0 (mean 2.5) Mitral valves: 2.5-3.5 (mean 3.0)	Some recommendation for limited anticoagulation for mitral valves
Increased risk of hemorrhage: 1-2%/yr	Decreased risk of hemorrhage

## Summary of Valvular Disease

Table 14. Valvular Heart Disease

### Aortic Stenosis (AS)

#### Etiology

Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease

#### Definition

Normal aortic valve area = 3–4 cm<sup>2</sup>

Mild AS 1.5 to 3 cm<sup>2</sup>

Moderate AS 1.0 to 1.5 cm<sup>2</sup>

Severe AS <1.0 cm<sup>2</sup>

Critical AS <0.5 cm<sup>2</sup>

#### Pathophysiology

Outflow obstruction → increased EDP → concentric LVH → LV failure → CHF, subendocardial ischemia

#### Symptoms

Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema

#### Physical Exam

Narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI  
Auscultation: crescendo-decrescendo SEM radiating to R clavicle and carotid, musical quality at apex (Gallavardin phenomenon), S<sub>4</sub>, soft S<sub>2</sub> with paradoxical splitting, S<sub>3</sub> (late)

#### Investigations

ECG: LVH and strain, LBBB, LAE, AFib

CXR: post-stenotic aortic root dilatation, calcified valve, LVH, LAE, CHF

Echo: reduced valve area, pressure gradient, LVH, reduced LV function

#### Treatment

Asymptomatic: serial echos, avoid exertion

Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS

Surgery if: symptomatic or LV dysfunction

#### Surgical Options

Valve replacement: aortic rheumatic valve disease and trileaflet valve

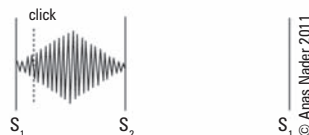
– prior to pregnancy (if AS significant)

– balloon valvuloplasty (in very young)

#### Interventional Options

Percutaneous valve replacement (transfemoral or transapical approach)

is an option in selected patients who are not considered good candidates for surgery



© Anas Nader 2011

### Aortic Regurgitation (AR)

#### Etiology

Supravalvular: aortic root disease (Marfan's, atherosclerosis and dissecting aneurysm, connective tissue disease)

Valvular: congenital (bicuspid aortic valve, large VSD), IE

Acute Onset: IE, aortic dissection, trauma, failed prosthetic valve

#### Pathophysiology

Volume overload → LV dilatation → increased SV, high sBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)

#### Symptoms

Usually only becomes symptomatic late in disease when LV failure develops

Dyspnea, orthopnea, PND, syncope, angina

#### Physical Exam

Waterhammer pulse, bisferiens pulse, femoral-brachial sBP >20 (Hill's test wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex

Auscultation: early decrescendo diastolic murmur at LLSB (cusp pathology) or RLSB (aortic root pathology), best heard sitting, leaning forward, on full expiration, soft S<sub>1</sub>, absent S<sub>2</sub>, S<sub>3</sub> (late)

#### Investigations

ECG: LVH, LAE

CXR: LVH, LAE, aortic root dilatation

Echo/TTE: quantify AR, leaflet or aortic root anomalies

Cath: if >40 yr and surgical candidate – to assess for ischemic heart disease

Exercise testing: hypotension with exercise

#### Treatment

Asymptomatic: serial echos, afterload reduction (e.g. ACEI, nifedipine, hydralazine)

Symptomatic: avoid exertion, treat CHF

Surgery if: NYHA class III–IV CHF; LV dilatation and/or LVEF <50% with/without symptoms

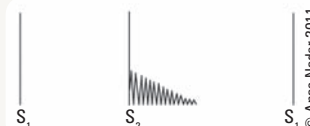
#### Surgical Options

Valve replacement: most patients

Valve repair: very limited role

Aortic root replacement (Bentall procedure):

– when ascending aortic aneurysm present, valved conduit used



© Anas Nader 2011

### Mitral Stenosis (MS)

#### Etiology

Rheumatic disease most common cause, congenital (rare)

#### Definition

Severe MS is mitral valve area (MVA)

<1.2 cm<sup>2</sup>

#### Pathophysiology

MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF; worse with AFib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)

#### Symptoms

SOB on exertion, orthopnea, fatigue, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)

#### Physical Exam

AFib, no "a" wave on JVP; left parasternal lift, palpable diastolic thrill at apex

Auscultation: mid-diastolic rumble at apex, best heard with bell in left lateral decubitus position following exertion, loud S<sub>1</sub>, OS following loud P<sub>2</sub> (heard best during expiration), long diastolic murmur and short A2–OS interval correlate with worse MS

#### Investigations

ECG: NSR/AFib, LAE (P mitrale), RVH, RAD

CXR: LAE, CHF, mitral valve calcification

Echo/TTE: shows restricted opening of mitral valve

Cath: indicated in concurrent CAD if >40 yr (male) or >50 yr (female)

#### Treatment

Avoid exertion, fever (increased LA pressure), treat AFib and CHF, increase diastolic filling time (β-blockers, digitalis)

Surgery if: NYHA class III–IV CHF and failure of medical therapy

#### Invasive Options

Percutaneous balloon valvuloplasty: young rheumatic pts and good leaflet morphology (can be determined by echo), asymptomatic pts with moderate-severe MS, pulmonary HTN

Contraindication: left atrial thrombus, moderate MR

Open Mitral Commissurotomy: if mild calcification + leaflet/chordal thickening

– restenosis in 50% pts in 8 yr

Valve replacement: indicated in moderate-severe calcification and severely scarred leaflets



© Anas Nader 2011

### Mitral Regurgitation (MR)

#### Etiology

Mitral valve prolapse, congenital cleft leaflets, LV dilatation/aneurysm (CHF, DCM, myocarditis), IE abscess, Marfan's syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease

Pathophysiology  
Reduced CO → increased LV and LA pressure → LV and LA dilatation → CHF and pulmonary HTN

Symptoms  
Dyspnea, PND, orthopnea, palpitations, peripheral edema

#### Physical Exam

Displaced hyperdynamic apex, left parasternal lift, apical thrill

Auscultation: holosystolic murmur at apex, radiating to axilla ± mid-diastolic rumble, loud S<sub>2</sub> (if pulmonary HTN), S<sub>3</sub>

#### Investigations

ECG: LAE, left atrial delay (bifid P waves), ± LVH

CXR: LVH, LAE, pulmonary venous HTN

Echo: etiology and severity of MR, LV function, leaflets

Swan-Ganz Catheter: prominent LA "v" wave

#### Treatment

Asymptomatic: serial echos

Symptomatic: decrease preload (diuretics), decrease afterload (ACEI) for severe MR and poor surgical candidates; stabilize acute MR with vasodilators before surgery

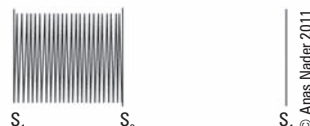
Surgery if: acute MR with CHF, papillary muscle rupture, NYHA class III–IV CHF, AF, increasing LV size or worsening LV function, earlier surgery if valve repairable (>90% likelihood) and patient is low-risk for surgery

#### Surgical Options

Valve repair: >75% of pts with MR and myxomatous mitral valve prolapse – annuloplasty rings, leaflet repair, chordae transfers/shorten/replacement

Valve replacement: failure of repair, heavily calcified annulus

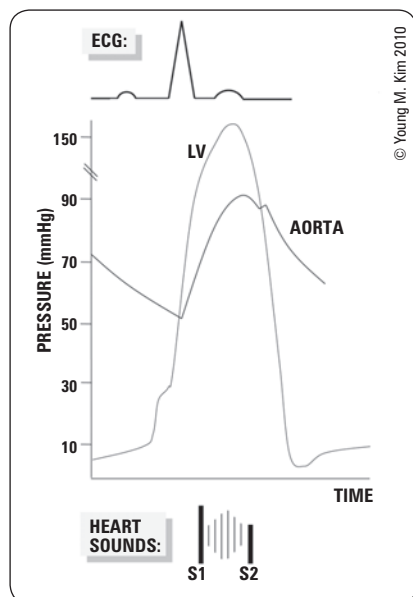
Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation



© Anas Nader 2011

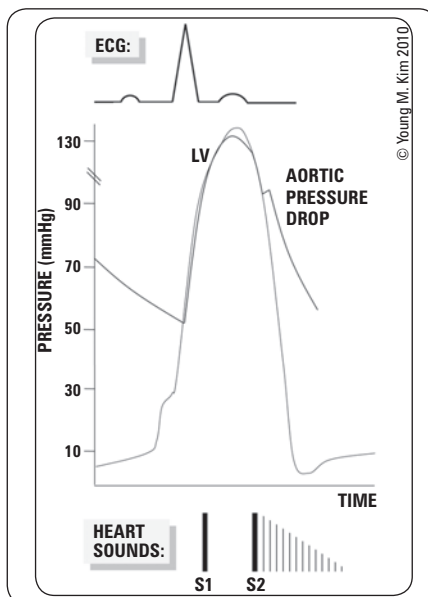
Table 14. Valvular Heart Disease (continued)

<p><b>Tricuspid Stenosis (TS)</b></p> <p><b>Etiology</b> Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS</p> <p><b>Pathophysiology</b> Increased RA pressure → right heart failure → decreased CO and fixed on exertion</p> <p><b>Symptoms</b> Peripheral edema, fatigue, palpitations</p> <p><b>Physical Exam</b> Prominent "a" waves in JVP, +ve abdominojugular reflex, Kussmaul's sign, diastolic rumble 4th left intercostal space</p> <p><b>Investigations</b> ECG: RAE CXR: dilatation of RA without pulmonary artery enlargement Echo: diagnostic</p> <p><b>Treatment</b> Preload reduction (diuretics), slow HR Surgery if: only if other surgery required (e.g. mitral valve replacement)</p> <p><b>Surgical Options</b> Valve Replacement: – if severely diseased valve – bioprosthesis preferred</p>	<p><b>Tricuspid Regurgitation (TR)</b></p> <p><b>Etiology</b> RV dilatation, IE (particularly due to IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid</p> <p><b>Pathophysiology</b> RV dilatation → TR → further RV dilatation → right heart failure</p> <p><b>Symptoms</b> Peripheral edema, fatigue, palpitations</p> <p><b>Physical Exam</b> "cv" waves in JVP, +ve abdominojugular reflux, Kussmaul's sign, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift</p> <p><b>Investigations</b> ECG: RAE, RVH, AFib CXR: RAE, RV enlargement Echo: diagnostic</p> <p><b>Treatment</b> Preload reduction (diuretics) Surgery if: only if other surgery required (e.g. mitral valve replacement)</p> <p><b>Surgical Options</b> Annuloplasty (i.e. repair, rarely replacement)</p>
<p><b>Pulmonary Stenosis (PS)</b></p> <p><b>Etiology</b> Usually congenital, rheumatic disease (rare), carcinoid syndrome</p> <p><b>Pathophysiology</b> Increased RV pressure → RV hypertrophy → right heart failure</p> <p><b>Symptoms</b> Chest pain, syncope, fatigue, peripheral edema</p> <p><b>Physical Exam</b> Systolic murmur at 2nd left intercostal space accentuated by inspiration, pulmonary ejection click, right-sided S4</p> <p><b>Investigations</b> ECG: RVH CXR: prominent pulmonary arteries enlarged RV Echo: diagnostic</p> <p><b>Treatment</b> Balloon valvuloplasty if severe symptoms</p> <p><b>Surgical Options</b> Percutaneous or open balloon valvuloplasty</p>	<p><b>Pulmonary Regurgitation (PR)</b></p> <p><b>Etiology</b> Pulmonary HTN, IE, rheumatic disease, tetralogy of Fallot (post-repair)</p> <p><b>Pathophysiology</b> Increased RV volume → increased wall tension → RV hypertrophy → right heart failure</p> <p><b>Symptoms</b> Chest pain, syncope, fatigue, peripheral edema</p> <p><b>Physical Exam</b> Early diastolic murmur at LLSB, Graham Steell (diastolic) murmur 2nd and 3rd left intercostal space increasing with inspiration</p> <p><b>Investigations</b> ECG: RVH CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV Echo: diagnostic</p> <p><b>Treatment</b> Rarely requires treatment; valve replacement (rarely done)</p> <p><b>Surgical Options</b> Pulmonary valve replacement</p>
<p><b>Mitral Valve Prolapse (MVP)</b></p> <p><b>Etiology</b> Myxomatous degeneration of chordae, thick, bulky leaflets that crowd orifice, associated with Marfan's syndrome, pectus excavatum, straight back syndrome, other MSK abnormalities; &lt;3% of population</p> <p><b>Pathophysiology</b> Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms</p> <p><b>Symptoms</b> Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope</p> <p><b>Physical Exam</b> Auscultation: mid-systolic click (due to billowing of mitral leaflet into LA; tensing of redundant valve tissue); mid to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers</p> <p><b>Investigations</b> ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy Echo: systolic displacement of thickened mitral valve leaflets into LA</p> <p><b>Treatment</b> Asymptomatic: no treatment; reassurance Symptomatic: β-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if AFib</p> <p><b>Surgical Options</b> Mitral valve surgery (repair favoured over replacement) if symptomatic and significant MR</p>	



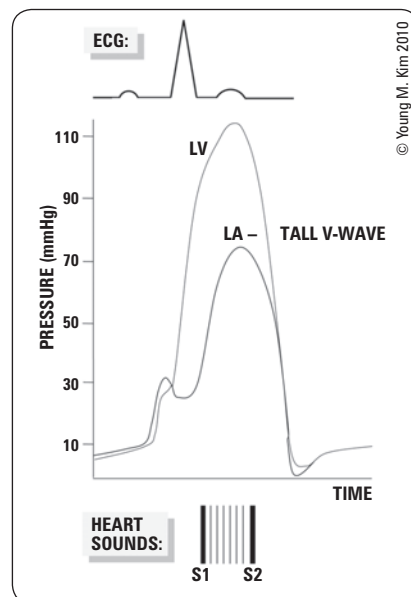
**Figure 37. Hemodynamics of aortic stenosis**

Stenosis across the aortic valve results in the generation of a significant pressure gradient between the left ventricle and the aorta and a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure hence diminishing S2.



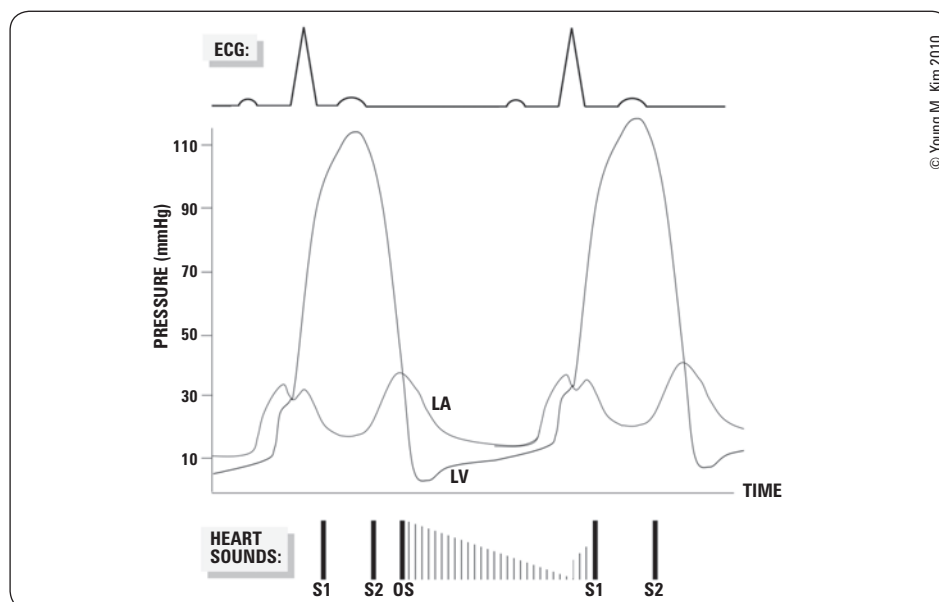
**Figure 38. Hemodynamics of aortic regurgitation**

Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2 is audible). The presence of regurgitant blood from the aorta increases left-ventricular end-diastolic volume.



**Figure 39. Hemodynamics of acute mitral regurgitation**

During systolic contraction, blood regurgitates from the left ventricle into the left atrium across the incompetent mitral valve resulting in an audible holosystolic murmur between S1 and S2. The portion of left ventricular end diastolic volume that regurgitates into the left atrial myocardium increases left atrial pressures resulting in a tall V-wave (in the JVP).



**Figure 40. Hemodynamics of mitral stenosis**

First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to mitral stenosis and the consequent generation of a pressure gradient across the left atrium and left ventricle. In diastole the stenotic mitral valve opens which corresponds to the opening snap (OS) and the passage of blood across the mitral stenosis results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible.

# Pericardial Disease

## Acute Pericarditis

### Etiology of Pericarditis/Pericardial Effusion

- idiopathic is most common: presumed to be viral
- infectious
  - viral: Coxsackie virus A, B (most common), echovirus
  - bacterial: *S. pneumoniae*, *S. aureus*
  - TB
  - fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma
- collagen vascular disease: SLE, polyarteritis, RA, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (sarcoid)

### Signs and Symptoms

- diagnostic triad: chest pain, friction rub, and ECG changes
- pleuritic chest pain: alleviated by sitting up and leaning forward
- pericardial friction rub: may be uni-, bi- or triphasic
- $\pm$  fever, malaise

### Investigations

- ECG: initially diffuse elevated ST segments  $\pm$  depressed PR segment, the elevation in the ST segment is concave upwards  $\rightarrow$  2-5 d later ST isoelectric with T wave flattening and inversion
- CXR: normal heart size, pulmonary infiltrates
- echo: performed to assess for pericardial effusion

### Treatment

- treat the underlying disease
- anti-inflammatory agents (high dose NSAIDs/ASA, steroids if severe or recurrent), analgesics

### Complications

- recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis



#### Acute Pericarditis Triad

- Chest Pain
- Friction Rub
- ECG Changes

## Pericardial Effusion

### Etiology

- transudative (serous)
- CHF, hypoalbuminemia/hypoproteinemia, hypothyroidism
- exudative (serosanguinous or bloody)
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
- physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

### Signs and Symptoms

- may be asymptomatic or similar to acute pericarditis
- dyspnea, cough
- extra-cardiac (esophageal/recurrent laryngeal nerve/tracheo-bronchial/phrenic nerve irritation)
- JVP increased with dominant "x" descent
- arterial pulse normal to decreased volume, decreased pulse pressure
- auscultation: distant heart sounds  $\pm$  rub
- Ewart's sign

### Investigations

- ECG: low voltage, flat T waves, electrical alternans
- CXR: cardiomegaly, rounded cardiac contour
- echo (procedure of choice): fluid in pericardial sac
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, neoplastic involvement

### Treatment

- mild: frequent observation with serial echos, treat underlying cause, anti-inflammatory agents
- severe: treat as in tamponade (see *Cardiac Tamponade*, C43)



#### Ewart's Sign

Bronchial breathing and dullness to percussion at the lower angle of the left scapula in pericardial effusion due to effusion compressing left lower lobe of lung.

## Cardiac Tamponade

### Etiology

- major complication of rapidly accumulating pericardial effusion
- cardiac tamponade is a clinical diagnosis
- any cause of pericarditis but especially trauma, malignancy, uremia, proximal aortic dissection with rupture

### Pathophysiology

- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

### Signs and Symptoms

- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in systolic BP >10 mmHg during quiet breathing)
- JVP “x” descent only, blunted “y” descent
- hepatic congestion/peripheral edema

### Investigations

- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- echo: pericardial effusion, compression of cardiac chambers (RA and RV) in diastole
- cardiac catheterization

### Treatment

- pericardiocentesis – echo-guided
- pericardiectomy
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO)
- IV fluid may increase CO
- treat underlying cause



#### Classic Quartet of Tamponade

- Hypotension
- Increased JVP
- Tachycardia
- Pulsus paradoxus



#### Beck's Triad

- Hypotension
- Increased JVP
- Muffled heart sounds



#### DDx Pulsus Paradoxus

- Constrictive pericarditis (rarely)
- Severe obstructive pulmonary disease (e.g. asthma)
- Tension pneumothorax
- PE
- Cardiogenic shock
- Cardiac tamponade

## Constrictive Pericarditis

### Etiology

- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease

### Signs and Symptoms

- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
  - ascites, hepatosplenomegaly, edema
- increased JVP, Kussmaul's sign (paradoxical increase in JVP with inspiration), Friedreich's sign (prominent “y” descent)
- BP usually normal (and usually no pulsus paradoxus)
- precordial examination: ± pericardial knock (early diastolic sound)
- see Table 15 for differentiation from cardiac tamponade

### Investigations

- ECG: non-specific – low voltage, flat T wave, ± AFib
- CXR: pericardial calcification, effusions
- echo/CT/MRI: pericardial thickening
- cardiac catheterization: equalization of end-diastolic chamber pressures (diagnostic)

### Treatment

- medical: diuretics, salt restriction
- surgical: pericardiectomy (only if refractory to medical therapy)
- prognosis best with idiopathic or infectious cause and worst in post-radiation. Death may result from heart failure

**Table 15. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade**

Characteristic	Constrictive Pericarditis	Cardiac Tamponade
JVP	“y” > “x”	“x” > “y”
Kussmaul's sign	Present	Absent
Pulsus paradoxus	Uncommon	Always
Pericardial knock	Present	Absent
Hypotension	Variable	Severe



## VASCULAR DISEASE

- see ESC Guidelines on the Diagnosis and Treatment of Peripheral Artery Diseases: Document Covering Atherosclerotic Disease of Extracranial Carotid and Vertebral, Mesenteric, Renal, Upper and Lower Extremity Arteries. "The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC)." *Eur Heart J* 2011;32(22):2851-2906 for details

## Peripheral Arterial Disease

### Peripheral Vascular Anatomy

- see Figure 41

### Acute Arterial Occlusion/Insufficiency

#### Definition

- acute occlusion/rupture of a peripheral artery
- urgent management required: treat within 6 h or irreversible ischemia and myonecrosis may result
- tends to be lower extremity > upper extremity; femoropopliteal > aortoiliac

#### Etiology and Risk Factors

**Table 16. Clinical Categories of Acute Limb Ischemia**

Grade	Category	Sensory loss	Motor deficit	Prognosis
I	Viable	None	None	No immediate threat
IIA	Marginally threatened	None or minimal (toes)	None	Salvageable if promptly treated
IIB	Immediately threatened	More than toes	Mild/moderate	Salvageable if promptly revascularized
III	Irreversible	Profound, anesthetic	Profound, paralysis (rigor)	Major tissue loss Amputation, Permanent nerve damage inevitable

#### Hypercoagulable States

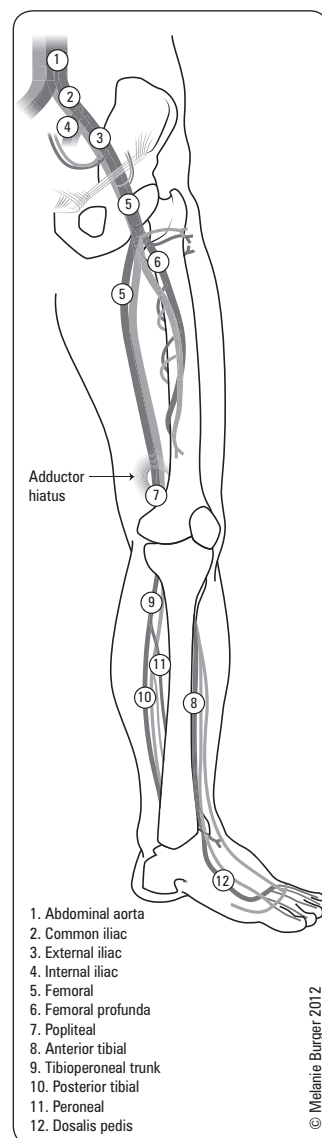
- congenital
  - group I (reduced anti-coagulants): anti-thrombin, protein C, protein S
  - group II: factor V leiden, prothrombin, factor VIII, hyper-homocysteinemia
- acquired: immobility, cancer, pregnancy/OCB, anti-phospholipid antibody syndrome, inflammatory disorders (e.g. IBD), myeloproliferative disorders (e.g. ET), nephrotic syndrome (acquired deficit in protein C and S), disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia with thrombosis (HITT)
- for presentation of embolus vs. thrombus see Table 17

#### Investigations

- history and physical exam: depending on degree of ischemia may have to forego investigations and go straight to OR
- ABI: extension of physical exam, easily performed at bedside
- ECG, troponin: rule out recent MI or arrhythmia
- CBC: rule out leukocytosis, thrombocytosis or recent drop in platelets in patients receiving heparin
- PT/INR: patient anticoagulated/sub-therapeutic INR
- echo: identify wall motion abnormalities, intracardiac thrombus, valvular disease, aortic dissection (type A)
- CT angiogram: underlying atherosclerosis, aneurysm, aortic dissection
- conventional catheter based angiography: can be obtained in OR; prelude to thrombolytics

#### Treatment

- immediate heparinization with 5000 IU bolus and continuous infusion to maintain PTT >60 s
- if absent power and sensation: emergent revascularization
- if present power and sensation: work-up (including angiogram)
- definitive treatment
  - embolus: embolectomy
  - thrombus: thrombectomy ± bypass graft ± endovascular therapy
  - irreversible ischemia: primary amputation
- identify and treat underlying cause
- continue heparin post-op, start warfarin post-op day 1 x 3 mo depending on underlying etiology



**Figure 41. Peripheral vascular anatomy**



#### Hypercoagulable State

##### Congenital

- Group I (reduced anticoagulants)
  - Antithrombin
  - Protein C
  - Protein S
- Group II (increased coagulants)
  - Factor V Leiden
  - Prothrombin
  - Factor VIII
  - Hyper-homocysteinemia

##### Acquired

- Immobility
- Cancer
- Pregnancy/OCB
- Antiphospholipid antibody syndrome
- Inflammatory disorders (e.g. IBD)
- Myeloproliferative disorders (e.g. ET)
- Nephrotic syndrome (acquired deficit in Protein C and S)
- Disseminated Intravascular Coagulation (DIC)
- Heparin-Induced Thrombocytopenia

**Table 17. Arterial Embolism vs. Thrombosis**

Presentation	Embolus	Thrombus
Onset	Acute	Progressive, acute-on-chronic
Loss of function/sensation	Prominent	Less profound (due to underlying collaterals)
Hx of claudication	No	Maybe
Atrophic changes	No	Maybe
Contralateral limb pulses	Classically normal	Decreased or absent

**Complications**

- compartment syndrome with prolonged ischemia; requires fasciotomy
- renal failure and multi-organ failure due to toxic metabolites from ischemic muscle

**Prognosis**

- 12-15% mortality rate
- 5-40% morbidity rate (amputation)

**Symptoms of Acute Limb Ischemia**

**6 Ps** – all may not be present

**Pain:** absent in 20% of cases

**Pallor:** within a few hours becomes mottled cyanosis

**Paresthesia:** light touch lost first then sensory modalities

**Paralysis/Power loss:** most important, heralds impending gangrene

**Polar/Poikilothermia** (cold)

**Pulselessness:** not reliable

## Chronic Arterial Occlusion/Insufficiency

**Etiology**

- predominantly due to atherosclerosis: primarily lower extremities

**Risk Factors**

- major: smoking, DM
- minor: HTN, hyperlipidemia, family history, obesity, sedentary lifestyle

**Clinical Features**

- claudication
  1. pain with exertion: usually in calves or any exercising muscle group
  2. relieved by short rest: 2 to 5 min, and no postural changes necessary
  3. reproducible: same distance to elicit pain, same location of pain, same amount of rest to relieve pain
- critical limb ischemia
  1. includes rest pain, night pain, tissue loss (ulceration or gangrene)
  2. ankle pressure <40 mmHg, toe pressure <30 mmHg, ABI <0.40
- pulses may be absent at some locations, bruits may be present
- signs of poor perfusion: hair loss, hypertrophic nails, atrophic muscle, skin ulcerations and infections, slow capillary refill, prolonged pallor with elevation and rubor on dependency, venous troughing (collapse of superficial veins of foot)
- other manifestations of atherosclerosis: CVD, CAD, impotence, splanchnic ischemia

**Investigations**

- non-invasive
  - routine bloodwork, fasting metabolic profile
  - ABI: take highest brachial and highest ankle [dorsalis pedis (DP) or posterior tibial (PT)] pressures for each side generally
    - ♦ ABI <0.90 abnormal, rest pain appears at <0.3 (see Table 18)
  - CTA and MRA: excellent for large arteries (aorta, iliac, femoral, popliteal), may have difficulty with tibial arteries (especially in the presence of disease). Both require IV injection of nephrotoxic contrast (iodinated contrast for CT, gadolinium for MR)
- invasive
  - arteriography: superior resolution to CTA/MRA, better for tibial arteries, can be done intraoperatively

**Differential of Claudication****Vascular**

- Atherosclerotic disease
- Vasculitis (e.g. Buerger's disease, Takayasu's arteritis)
- Diabetic neuropathy
- Venous disease (e.g. DVT, varicose veins)
- Popliteal entrapment syndrome (e.g. Baker's cyst, tumour)

**Neurologic**

- Neurospinal disease (e.g. spinal stenosis)
- Reflex sympathetic dystrophy

**MSK**

- Osteoarthritis
- Rheumatoid arthritis/connective tissue disease
- Remote trauma

**Table 18. Ankle-Brachial Indices**

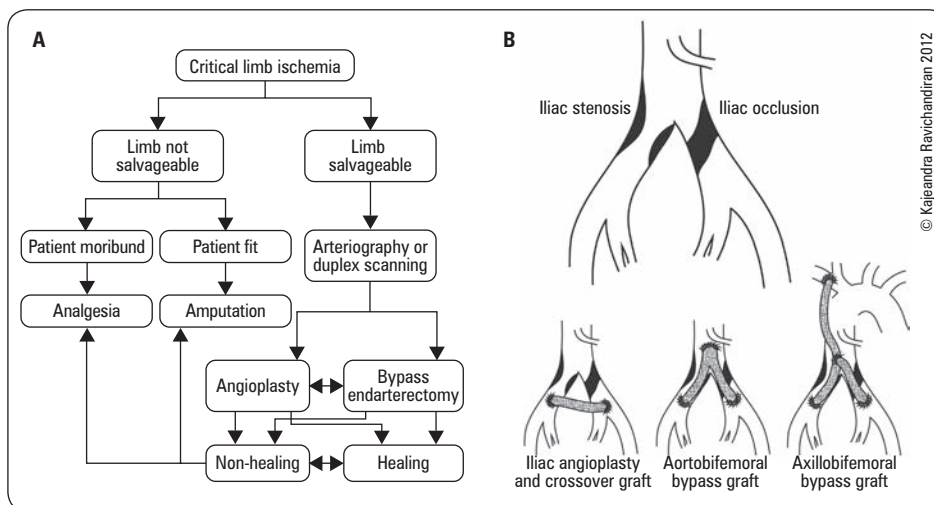
ABI Recording	Degree of Ischemia
>1.2	Suspect wall calcification (most common in diabetics)
>0.95	Normal/no ischemia
0.50 – 0.8	Claudication range
<0.4	Possible critical ischemia

**Treatment** (see Figure 42)

- conservative
  - risk factor modification (smoking cessation, treatment of HTN, hyperlipidemia, DM)
  - exercise program: improves collateral circulation, oxygen extraction at the muscle level
  - foot care (especially in DM): keep wounds clean/dry, avoid trauma and pressure on wounds
- pharmacotherapy
  - antiplatelet agents (ECASA, clopidogrel or more rarely ticlopidine)
  - cilostazol (cAMP-phosphodiesterase inhibitor with antiplatelet and vasodilatory effects) – improves walking distance for some patients with claudication (not available in Canada)
- surgical/endovascular
  - indications: severe lifestyle impairment, vocational impairment, critical ischemia
  - surgical options:
    - ♦ endovascular (stenting/angioplasty) (see [Medical Imaging](#), MI28)
    - ♦ endarterectomy: removal of plaque and repair with patch (usually distal aorta or common/profunda femoral)
    - ♦ bypass graft sites: aortofemoral, axillofemoral, femoropopliteal, distal arterial (see Figure 42)
      - graft choices: vein graft (reversed or in situ), synthetic – polytetrafluoroethylene graft (e.g. Gore-Tex®) or Dacron®
    - ♦ chemical sympathectomy: sympathetic plexus destroyed with EtOH injection into nerve plexus, may stimulate vasodilation (rarely effective)
    - ♦ amputation: if not suitable for revascularization, persistent serious infections/gangrene

**Prognosis**

- claudication: conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 yr, <4% will require amputation
- for patients with critical ischemia (rest pain, night pain, ulceration or gangrene): high risk of limb loss

**Figure 42. Treatment options for critical limb ischemia**

(A) Algorithm for the treatment of critical limb ischemia

(B) Surgical treatment options for the treatment of aortoiliac disease

Modified from Beard JD. Chronic lower limb ischemia. *BMJ*. 2000;320:854-857

## Hypertension

- see [Family Medicine](#), FM37



## Pulmonary Hypertension

- see [Respirology](#), R16



## Aortic Disease

- see 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease. *J Am Coll Cardiol* 2010;55(14):e27–e129 for details

## Aortic Anatomy

- see Figure 43

## Aortic Dissection

### Definition

- tear in aortic intima allowing blood to dissect into the media; acute <2 wk (initial mortality 1% per hour for type A dissections), chronic >2 wk (mortality levels up to 75–80%)

### Etiology

- most common: HTN → degenerative/cystic changes → damage to aortic media
- other: connective tissue disease (e.g. Marfan's, Ehlers-Danlos), cystic medial necrosis, atherosclerosis, congenital conditions (e.g. coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection (e.g. syphilis), trauma, arteritis (e.g. Takayasu's)

### Epidemiology

- incidence of 5.2 in 1 000 000
- male:female = 3.2:1
- small increased incidence in African-Canadians (related to higher incidence of HTN)
- lowest incidence in Asians
- peak incidence 50–65 yr old; 20–40 yr old with connective tissue diseases

### Clinical Features

- sudden onset tearing chest pain that radiates to back with:
  - HTN (75–85% of patients)
  - asymmetric BPs and pulses between arms (>30 mmHg difference indicates poor prognosis)
  - ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotids (ischemic stroke, Horner's syndrome), splanchnic (mesenteric ischemia), renal (AKI), peripheral (ischemic leg), intercostal vessels (spinal cord ischemia)
  - "unseating" of aortic valve cusps (new diastolic murmur in 20–30%)
  - rupture into pleura (dyspnea, hemoptysis) or peritoneum (hypotension, shock) or pericardium (cardiac tamponade)
  - syncope

### Investigations

- CXR
  - pleural cap (pleural effusion in lung apices)
  - widened mediastinum
  - left pleural effusion with extravasation of blood
- TEE: can visualize aortic valve and thoracic aorta but not abdominal aorta
- ECG: LVH ± ischemic changes, pericarditis, heart block
- CT (gold standard), aortography, MRA: 100% sensitive and specific
- bloodwork: lactate (r/o ischemic gut), amylase (r/o pancreatitis), troponin (r/o MI)

### Treatment

- pharmacologic
  - β-blocker to lower BP and decrease cardiac contractility
  - use nondihydropyridine calcium channel blocker if there is a clear contraindication to β-blockers
  - target sBP of 110 mmHg and HR of less than 60 bpm
  - ACEI and/or other vasodilators if insufficient BP or HR control
- surgical
  - urgent surgical consult if thoracic aortic dissection diagnosed or highly suspected
  - resection of segment with intimal tear
  - reconstitution of flow through true lumen
  - replacement of the affected aorta with prosthetic graft
  - correction of any predisposing factors

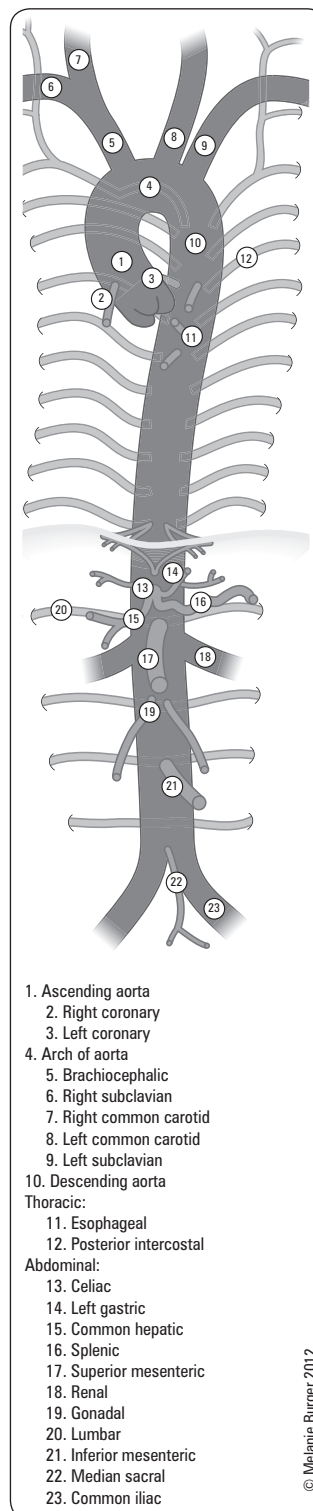


Figure 43. Aortic anatomy

- post-operative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
- 2/3 of patients die of operative or post-operative complications
- Type A: requires emergent surgery with cardiopulmonary bypass;
  - ♦ may require:
    - hypothermic circulation for transverse arch dissections
    - resuspension of aortic valve
    - aortic valve replacement
    - coronary re-implantation for aortic root involvement
  - ♦ initial mortality rate without surgery is 3% per h for first 24 h, 30% 1 wk, 80% 2 wk
- Type B: managed medically in absence of malperfusion syndrome
  - ♦ <10-20% require urgent operation for complications
  - ♦ treatment can be surgical or endovascular
- with treatment, 60% 5 yr survival, 40% 10 yr survival

## Aortic Aneurysm

### Definition of Aneurysm

- localized dilatation of an artery having a diameter at least 1.5 times that of the expected normal diameter
  - true aneurysm: involving all vessel wall layers (intima, media, adventitia)
  - false aneurysm (also known as pseudo-aneurysm): disruption of the aortic wall or the anastomotic site between vessel and graft with containment of blood by a fibrous capsule made of surrounding tissue
- aneurysms can rupture, thrombose, embolize, erode, and fistulize

### Classification

- thoracic aortic aneurysm (TAA): ascending, transverse arch, descending
- thoracoabdominal
- abdominal aortic aneurysm (AAA): 90-98% are infrarenal

### Etiology

- degenerative (atherosclerotic)
- traumatic
- mycotic (*Salmonella*, *Staphylococcus*, usually suprarenal aneurysms)
- connective tissue disorder (Marfan syndrome, Ehlers-Danlos syndrome)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic aneurysms are associated with bicuspid aortic valve
- risk factors: smoking, HTN, age >70, family history

### Epidemiology

- incidence 4.7 to 31.9 per 100 000 for AAA and 5.9 per 100 000 for TAA
- high risk groups
  - 65 yr and older
  - male:female = 3.8:1
  - PVD, CAD, CVD
  - family history of AAA

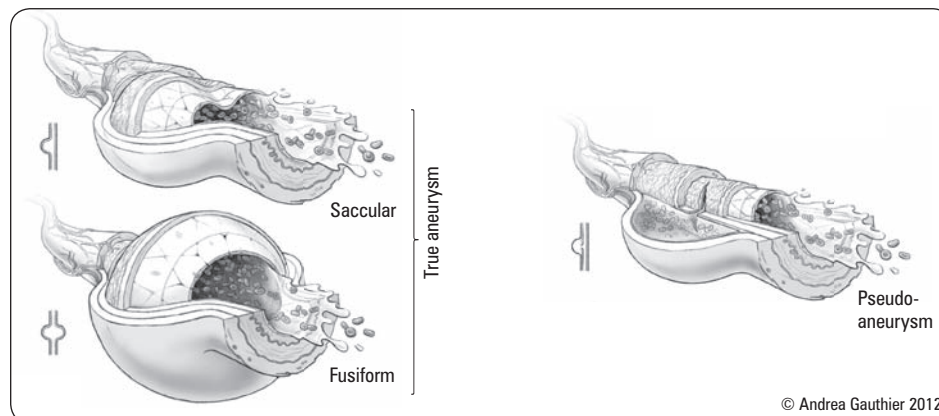


Figure 45. Classification of aneurysms

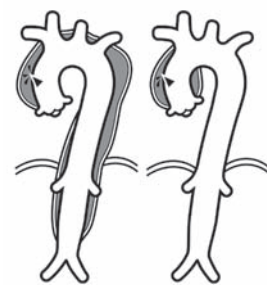


### Does This Patient have an Acute Thoracic Aortic Dissection

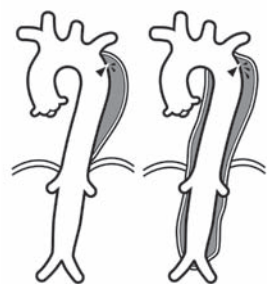
JAMA 2002;287:2262-2272

	LR + (95% CI)	LR - (95% CI)
<b>History</b>		
Hypertension	1.6 (1.2-2.0)	0.5 (0.3-0.7)
Sudden onset of pain*	1.6 (1.0-2.4)	0.3 (0.2-0.5)
"Tearing" or "ripping" pain	1.2-11	0.4-1.0
Migratory pain	-7.6	0.6-1.0
<b>Physical Examination</b>		
Pulse deficit*	5.7 (1.4-23)	0.7 (0.6-0.9)
Focal neurologic deficits	6.6-33	0.7-0.9
Diastolic murmur	1.4 (1.0-2.0)	0.9 (0.8-1.0)
<b>Investigation</b>		
Enlarged aorta or wide mediastinum*	2.0 (1.4-3.1)	0.3 (0.2-0.4)

\*Combination of findings increases LR+: if no findings LR+ 0.1, if one LR+ 0.5, if two LR+ 5.3, if three LR+ 6.6



DeBakey: Type I: 50% Type II: 35%  
Stanford: Type A



DeBakey: Type IIIA 15% Type IIIB  
Stanford: Type B

Figure 44. Classification of aortic dissection (black arrow indicates where the dissection begins)



ACC/AHA 2005 Guidelines define an AAA when the minimum AP diameter of abdominal aorta  $\geq 3.0$  cm.

© Andrea Gauthier 2012



## Clinical Features

- common presentation: due to acute expansion or disruption of wall
  - syncope
  - pain (chest, abdominal, flank, back)
  - hypotension
  - palpable pulsatile mass above the umbilicus, pulsatile abdominal mass in two directions (expandable)
  - airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis (indicates thoracic or thoracoabdominal aortic aneurysm)
  - distal pulses may be intact
- 75% asymptomatic (discovered incidentally)
- uncommon presentation
  - ureteric obstruction and hydronephrosis (often with inflammatory aortic aneurysm)
  - GI bleed (duodenal mucosal hemorrhage, aortoduodenal fistula)
  - aortocaval fistula
  - distal embolization (blue toe syndrome)
- associated diseases
  - HTN, PVD, CAD, COPD, renal insufficiency
- most commonly in the abdominal aorta (50% abdominal aorta, 40% thoracic aorta, 10% ascending aorta)

## Investigations

- bloodwork: CBC, electrolytes, urea, creatinine, PTT, INR, type and cross
- abdominal U/S (100% sensitive, up to  $\pm 0.6$  cm accuracy in size determination)
- CT (accurate visualization, size determination)
- MRI (accurate visualization, limited access)
- aortogram (only for EVAR)
- Doppler/duplex (r/o vascular tree aneurysms elsewhere, e.g. popliteal)

## Treatment

- conservative
  - cardiovascular risk factor reduction: smoking cessation; control of HTN, DM, and hyperlipidemia
  - regular exercise
  - watchful waiting, U/S every 6 mo to 3 yr depending on size and location
- surgical
  - when risk of rupture greater than or equal to risk of surgery ( $>5.5$  cm)
  - risk of rupture depends on
    - ♦ size
    - ♦ rate of enlargement (if  $>0.4$  cm/yr)
    - ♦ symptoms, comorbidities (HTN, COPD, dissection), smoking
  - elective AAA repair mortality 2-5%; elective TAA repair mortality  $<10\%$  (highest with proximal aortic and thoracoabdominal repairs)
  - consider revascularization for patients with CAD before elective repair of aneurysm
  - indications
    - ♦ general: ruptured, symptomatic, mycotic, associated with acute Type A dissection or complicated Type B dissection or when risk of rupture is greater than risk of surgery (size  $>5.5$  cm or  $>2\times$  normal lumen size)
    - ♦ ascending thoracic aortic aneurysms
      - symptomatic, enlarging, diameter  $>5.5$  cm or  $>2\times$  normal lumen size,  $>4.5$  cm and aortic regurgitation (annuloaortic ectasia);  $\geq 4.5$ -5 cm in Marfan syndrome
  - contraindications: life expectancy  $<1$  yr, terminal disease (e.g. cancer), significant comorbidities (e.g. recent MI, unstable angina), decreased mental acuity, advanced age
  - surgical options
    - ♦ open surgery (laparotomy or retroperitoneal) with graft replacement
      - possible complications
      - early: renal failure, spinal cord injury (paraparesis or paraplegia), impotence, arterial thrombosis, anastomotic rupture or bleeding, peripheral emboli
      - late: graft infection/thrombosis, aortoenteric fistula, anastomotic (pseudo) aneurysm
    - ♦ endovascular aneurysm repair (EVAR)
      - newer procedure; high success rates in patients with suitable anatomy and experienced centres
      - advantages: decreased morbidity and mortality, procedure time, need for transfusion, ICU admissions, length of hospitalization, and recovery time
      - disadvantages: endoleak rates as high as 20-30%, device failure increasing as longer follow-up periods are achieved, re-intervention rates 10-30%, cost-effectiveness is an issue (devices are very expensive), radiation exposure
      - complications
        - early: immediate conversion to open repair, groin hematoma, arterial thrombosis, iliac artery rupture, and thromboemboli
        - late: endoleak (see sidebar), severe graft kinking, migration, thrombosis, rupture of aneurysm



### Classic Triad of Ruptured AAA

- Pain
- Hypotension
- Pulsatile abdominal mass



### CCS PAD Guidelines 2006 recommend AAA screening among:

- Men aged 65-74
- Women aged 65 with cardiovascular disease and positive family history of AAA
- Men aged 50 and above with a positive family history

### CCS PAD Guidelines 2006 recommend AAA follow-up based on initial size:

Size	Guideline
$<3.0$ cm	Repeat ultrasound follow-up in 3-5 yr
3.1-3.4 cm	Repeat ultrasound in 3 yr
3.5-3.9 cm	Repeat ultrasound in 2 yr
4.0-4.5 cm	Repeat ultrasound in 1 yr
$\geq 4.5$ cm	Referral to vascular surgeon and repeat ultrasound every 6 mo
If $>1$ cm growth in one yr	Referral to vascular surgeon for consideration of repair



### Management of Ruptured AAA

- ABCs
- No imaging (hemodynamically unstable)
- Straight to OR (confirm diagnosis by laparotomy)
- Crossmatch 10 units packed RBCs



### Risk of AAA Rupture

Size (diameter)	1-yr rupture risk
$<4$ cm	0%
4-4.9 cm	1%
5-5.9 cm	5-10%
6-6.9 cm	10-20%
7-7.9 cm	20-40%



### Endoleak Types

**Definition:** persistent blood flow into the aneurysm sac

**Type I:** ineffective seal at ends of graft

**Type II:** backflow from collateral vessels

**Type III:** ineffective seal of graft joints or rupture of graft fabric

**Type IV:** flow through pores of graft fabric



# Peripheral Venous Disease

## Deep Venous Thromboembolism

- see [Hematology](#), H31



## Superficial Venous Thrombosis (SVT)

### Definition

- erythema, induration, and tenderness along the superficial vein; usually spontaneous but can follow venous cannulation

### Etiology

- infectious: suppurative phlebitis (complication of IV cannulation; associated with fever/chills)
- trauma
- inflammatory: varicose veins, migratory superficial thrombophlebitis, Buerger's disease, SLE
- hematologic: polycythemia, thrombocytosis
- neoplastic: occult malignancy (especially pancreatic)
- idiopathic



Migratory superficial thrombophlebitis is often a sign of underlying malignancy ("Trousseau's disease").

### Clinical Features

- most common in greater saphenous vein and its tributaries
- pain and cord-like swelling along course of involved vein
- areas of induration, erythema, and tenderness correspond to dilated and often thrombosed superficial veins
- complications
  - simultaneous DVT (up to 20% of cases), PE (rare unless DVT)
  - recurrent superficial thrombophlebitis

### Investigations

- non-invasive tests (e.g. Doppler) to exclude associated DVT

### Treatment

- conservative
  - moist heat, compression bandages, mild analgesic, anti-inflammatory and anti-platelet (e.g. ASA), LMWH, ambulation
- surgical excision of involved vein
  - indication: failure of conservative measures (symptoms that persist over 2 wk)
  - suppurative thrombophlebitis: broad-spectrum IV antibiotics and excision

## Varicose Veins

### Definition

- distention of tortuous superficial veins resulting from incompetent valves in the deep, superficial, or perforator systems
- distribution: greater saphenous vein and tributaries (most common), esophagus, anorectum, scrotum

### Etiology

- primary
  - main factor: inherited structural weakness of valves
  - contributing factors: increasing age, female gender, OCP use, occupations requiring long hours of standing, pregnancy, obesity
- secondary
  - malignant pelvic tumours with venous compression
  - congenital anomalies, arteriovenous fistulae

### Epidemiology

- primary varicose veins are the most common form of venous disorder of lower extremity
- 10-20% of population

**Clinical Features**

- diffuse aching, fullness/tightness, nocturnal cramping
- aggravated by prolonged standing (end of day), premenstrual
- visible long, dilated and tortuous superficial veins along thigh and leg
- ulceration, hyperpigmentation, and induration (secondary varicosities)
- Brodie-Trendelenberg test (valvular competence test)
- with patient supine, raise leg and compress saphenous vein at thigh, have patient stand – if veins fill quickly from top down then incompetent valves; use multiple tourniquets to localize incompetent veins

**Complications**

- recurrent superficial thrombophlebitis
- hemorrhage: external or subcutaneous
- ulceration, eczema, lipodermatosclerosis, and hyperpigmentation

**Treatment**

- largely a cosmetic problem
- conservative: elevation of leg and/or elastic compression stockings
- surgical: high ligation and stripping of the long saphenous vein and its tributaries, ultrasound-guided foam sclerotherapy, endovenous laser therapy (EVLT)
- indications for surgery: symptomatic varix (pain, bleeding, recurrent thrombophlebitis), tissue changes (hyperpigmentation, ulceration), failure of conservative treatment, cosmetics

**Prognosis**

- benign course with predictable complications
- almost 100% symptomatic relief with treatment if varicosities are primary
- good cosmetic results with treatment
- significant post-operative recurrence, especially with sclerosing agent injection

## Chronic Venous Insufficiency (CVI)

**Definition**

- venous insufficiency and skin damage

**Etiology**

- calf muscle pump dysfunction and valvular incompetence (valvular reflux) due to phlebitis, varicosities, or DVT
- venous obstruction
- AV fistulas, venous malformations

**Clinical Features**

- pain (most common), ankle and calf edema – relieved by foot elevation
- pruritus, brownish hyperpigmentation (hemosiderin deposits)
- stasis dermatitis, subcutaneous fibrosis if chronic (lipodermatosclerosis)
- ulceration: shallow, above medial malleolus, weeping (wet), painless, irregular outline
- signs of DVT/varicose veins/thrombophlebitis

**Investigations**

- ambulatory venous pressure measurement (gold standard)
- Doppler U/S (most commonly used)
- photoplethysmography

**Treatment**

- conservative
  - elastic compression stockings, leg elevation, avoid prolonged sitting/standing
  - ulcers: zinc-oxide wraps, split-thickness skin grafts, antibiotics, debridement
- surgical
  - if conservative measures fail, or if recurrent/large ulcers
  - surgical ligation of perforators in region of ulcer, (GSV/LSV ligation and stripping)

## Lymphedema

### Definition

- obstruction of lymphatic drainage resulting in edema with high protein content

### Etiology

- primary: Milroy's syndrome (congenital hereditary lymphedema)
- secondary:
  - infection: filariasis (#1 cause worldwide), post-operative
  - malignant infiltration: axillary, groin or intrapelvic
  - radiation/surgery (axillary, groin lymph node removal): #1 cause in North America

### Clinical Features

- classically non-pitting edema
- impaired limb mobility, discomfort/pain, psychological distress

### Treatment

- avoid limb injury (can precipitate or worsen lymphedema)
- skin hygiene
  - daily skin care with moisturizers
  - topical treatment of fungal infection; systemic treatment of bacterial infection
- external support
  - intensive: compression bandages
  - maintenance: lymphedema sleeve
- exercise
  - gentle daily exercise of affected limb, gradually increasing ROM
  - must wear a compression sleeve/bandages when doing exercises
- massage and manual lymph drainage therapy

### Prognosis

- if left untreated becomes resistant to treatment due to subcutaneous fibrosis
- cellulitis causes rapid increase in swelling: can lead to sepsis and death

## Common Medications

**Table 19. Commonly Used Cardiac Therapeutics**

Drug Class	Examples	Mechanism of Action	Indications	Side Effects	Contraindications
ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)					
	enalapril (Vasotec®), perindopril (Coversyl®), ramipril (Altace®) lisinopril (Zestril®)	Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis	HTN, CAD, CHF, post-MI, DM	Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema	Bilateral renal artery stenosis, pregnancy, caution in decreased GFR
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)					
	candesartan, irbesartan, valsartan	Block AT II receptors, causing similar effects to ACEI	Same as ACEI, although evidence is generally less for ARBs. Often used when ACEI are not tolerated	Similar to ACEI, but do not cause dry cough	Same as ACEI
DIRECT RENIN INHIBITORS (DRIs)					
	aliskiren	Directly blocks renin thus inhibiting the conversion of angiotensinogen to angiotensin I. This also causes a decrease in AT II	HTN (exact role of this drug remains unclear)	Diarrhea, hyperkalemia (higher risk if used with an ACEI), rash, cough, angioedema, reflux, hypotension, rhabdomyolysis, seizure	Pregnancy, severe renal impairment
β-BLOCKERS					
β1 antagonists	atenolol, metoprolol, bisoprolol	Block β-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand, slow conduction through the AV node	HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AFib, SVT	Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud's phenomenon and claudication	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW. Caution in asthma, claudication, Raynaud's phenomenon, and decompensated CHF
β1/β2 antagonists	propranolol				
α1/β1/β2 antagonists	labetalol, carvedilol				
β1 antagonists with intrinsic sympathomimetic activity	acebutalol				
CALCIUM CHANNEL BLOCKERS (CCBs)					
Benzothiazepines Phenylalkylamines (non-dihydropyridines)	diltiazem verapamil	Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers Also vasodilate	HTN, CAD, SVT, diastolic dysfunction	Hypotension, bradycardia, edema Negative inotrope	Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW, CHF
Dihydropyridines	amlodipine (Norvasc®), nifedipine (Adalat®), felodipine (Plendil®)	Block smooth muscle calcium channels causing peripheral vasodilation	HTN	Hypotension, edema, flushing, headache, light-headedness	Severe aortic stenosis and liver failure
DIURETICS					
Thiazides	hydrochlorothiazide, chlorthalidone metolazone	Reduce Na <sup>+</sup> reabsorption in the distal convoluted tubule (DCT)	HTN (drugs of choice for uncomplicated HTN)	Hypotension, hypokalemia, polyuria	Sulfa allergy, pregnancy
Loop diuretics	furosemide (Lasix®)	Blocks Na <sup>+</sup> /K <sup>+</sup> -ATPase in the loop of Henle	CHF, pulmonary or peripheral edema	Hypovolemia, hypokalemic metabolic alkalosis	Hypovolemia, hypokalemia
Aldosterone receptor antagonists	spironolactone, eplerenone	Antagonize aldosterone receptors	HTN, CHF, hypokalemia	Edema, hyperkalemia, gynecomastia	Renal insufficiency, hyperkalemia, pregnancy
INOTROPES					
	digoxin (Lanoxin®)	Inhibit Na <sup>+</sup> /K <sup>+</sup> -ATPase, leading to increased intracellular Na <sup>+</sup> and Ca <sup>2+</sup> concentration and increased myocardial contractility. Also slows conduction through the AV node	CHF, AFib	AV block, tachyarrhythmias, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, nausea and vomiting	2nd or 3rd degree AV block, hypokalemia, WPW

**Table 19. Commonly Used Cardiac Therapeutics** (continued)

Drug Class	Examples	Mechanism of Action	Indications	Side Effects	Contraindications
<b>ANTICOAGULANTS</b>					
Coumarins	warfarin (Coumadin®)	Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X	AFib, LV dysfunction, prosthetic valves	Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis	Recent surgery or bleeding, bleeding diathesis, pregnancy
Heparins	Unfractionated heparin LMWHs: dalteparin, enoxaparin, tinzaparin	Antithrombin III agonist, leading to decreased clotting factor activity	Acute MI; when immediate anticoagulant effect needed	Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs)	Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)
Direct thrombin inhibitors	dabigatran, melagatran	Competitive, direct thrombin inhibitor; thrombin enables fibrinogen conversion to fibrin during the coagulation cascade, thereby preventing thrombus development	Atrial fibrillation	Bleeding, GI upset	Severe renal impairment, recent surgery, active bleeding
Direct Factor Xa inhibitors	rivaroxaban	Direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways	Atrial fibrillation	Bleeding, GI upset, elevated liver enzymes	Hepatic disease, active bleeding, bleeding diathesis, pregnancy, lactation
<b>ANTIPLATELETS</b>					
Salicylates	ASA (Aspirin®)	Irreversibly acetylates platelet COX-1, preventing thromboxane A2-mediated platelet aggregation	CAD, acute MI, post-MI, post-PCI, CABG	Bleeding, GI upset, GI ulceration, impaired renal perfusion	Active bleeding or peptic ulcer disease (PUD)
Thienopyridines	clopidogrel (Plavix®) ticlopidine (Ticlid®)	Block platelet ADP receptors	Acute MI, post-MI, post-PCI, CABG	Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)	Active bleeding or PUD
GPIIb/IIIa inhibitors	eptifibatide, tirofiban, abciximab	Block binding of fibrinogen to Gp IIb/IIIa	Acute MI, particularly if PCI is planned	Bleeding	Recent surgery or bleeding, bleeding diathesis
<b>THROMBOLYTICS</b>					
	alteplase, reteplase, tenecteplase, streptokinase	Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin	Acute STEMI	Bleeding	See Table 6, C25
<b>NITRATES</b>					
	nitroglycerin	Relax vascular smooth muscle, producing venous and arteriolar dilation	CAD, MI, CHF (isosorbide dinitrate plus hydralazine)	Headache, dizziness, weakness, postural hypotension	Concurrent use of cGMP phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure
<b>LIPID LOWERING AGENTS</b>					
Statins	atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Meracor®)	Inhibit HMG CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis	Dyslipidemia (1° prevention of CAD), CAD, post-MI	Myalgia, rhabdomyolysis, abdominal pain	Liver or muscle disease

## Antiarrhythmics

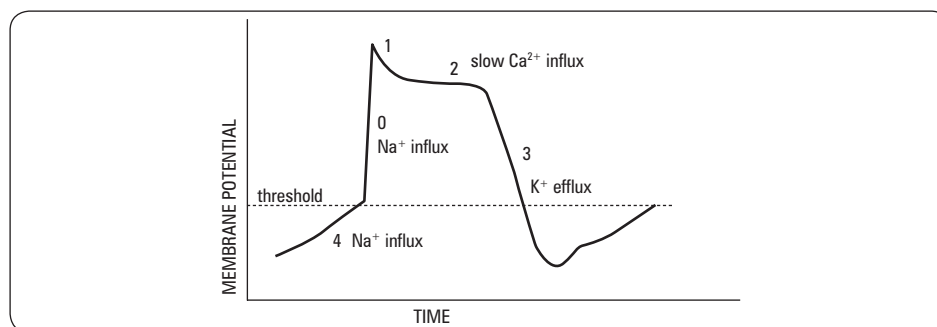


Figure 46. Representative cardiac action potential

Table 20. Antiarrhythmic\* Drugs (Vaughan-Williams Classification)

Class	Agent	Indications	Side Effects	Mechanism of Action
Ia	quinidine procainamide disopyramide	SVT, VT	Torsades de Pointes (all Ia), diarrhea Lupus-like syndrome Anticholinergic effects	Moderate Na <sup>+</sup> channel blockade Slows phase 0 upstroke Prolongs repolarization, slowing conduction
Ib	lidocaine mexiletine	VT	Confusion, stupor, seizures GI upset, tremor	Mild Na <sup>+</sup> channel blockade Shortens phase 3 repolarization
Ic	propafenone flecainide encainide	SVT, VT AFib	Exacerbation of VT (all Ic) Negative inotropy (all Ic) Bradycardia and heart block (all Ic)	Marked Na <sup>+</sup> channel blockade Markedly slows phase 0 upstroke
II	propranolol metoprolol, etc.	SVT, AFib	Bronchospasm, negative inotropy, bradycardia, AV block, impotence, fatigue	β-blocker Decreases phase 4 depolarization
III	amiodarone** sotalol	SVT, VT AFib SVT, VT, AFib	Photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR Torsades de Pointes, bradycardia, heart block, β-blocker side effects	Blocks K <sup>+</sup> channel Prolongs phase 3 repolarization, which prolongs refractory period
IV	verapamil diltiazem	SVT AFib	Bradycardia, AV block Hypotension	Calcium channel blocker Slows phase 4 spontaneous depolarization, slowing AV node conduction

\*All antiarrhythmics have potential to be proarrhythmic

\*\*Amiodarone has class I, II, III, and IV properties



### Antiarrhythmic Drug Classification

Some Block Potassium Channels

- I – Sodium channel blocker
- II – β-Blocker
- III – Potassium channel blocker
- IV – CCB

Table 21. Actions of α and β Adrenergic Receptors

	α RECEPTORS		β RECEPTORS	
Target System	α1	α2	β1	β2
Cardiovascular	Constriction of vascular smooth muscle Constriction of skin, skeletal muscle, and splanchnic vessels  Increased myocardial contractility Decreased heart rate	Same as α1   Peripherally act to modulate vessel tone Vasoconstrict and dilate; oppose α1 vasoconstrictor activity	Increased myocardial contractility Accelerate SA node Accelerate ectopic pacemakers	Decreased vascular smooth muscle tone
Respiratory				Bronchodilation
Dermal	Pilomotor smooth muscle contraction Apocrine constriction			
Ocular	Radial muscle contraction		Ciliary muscle relaxation	
Gastrointestinal	Inhibition of myenteric plexus Anal sphincter contraction			
Genitourinary	Pregnant uterine contraction Penile and seminal vesicle ejaculation Urinary bladder contraction	Smooth muscle wall relaxation	Stimulation of renal renin release	Bladder wall relaxation Uterine relaxation
Metabolic	Stimulate liver gluconeogenesis and glycogenolysis at the liver	Same as α1 Fat cell lipolysis	Fat cell lipolysis Glycogenolysis	Gluconeogenesis Fat cell lipolysis

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)



Table 22. Commonly Used Drugs that Act on  $\alpha$  and  $\beta$  Adrenergic Receptors

Mechanism of Action	$\alpha$ RECEPTORS			$\beta$ RECEPTORS		
	$\alpha 1$	$\alpha 1$ and $\alpha 2$	$\alpha 2$	$\beta 1$	$\beta 1$ and $\beta 2$	$\beta 2$
<b>Agonist</b>	Phenylephrine Methoxamine	Epinephrine Norepinephrine	Clonidine Methyldopa	Norepinephrine Dobutamine	Isoproterenol Epinephrine	Albuterol Terbutaline
<b>Antagonist</b>	Prazosin Phenoxybenzamine	Phentolamine	Yohimbine Mirtazipine	Metoprolol Acebutolol Alprenolol Atenolol Esmolol	Propranolol Timolol Nadolol Pindolol Carvedilol	Butoxamine

Adapted from the Family Practice Notebook (<http://www.fpnotebook.com/NEU194.htm>)

## Landmark Cardiac Trials

Trial	Reference	Results
<b>ISCHEMIC HEART DISEASE</b>		
ASCOT-LLA	<i>Lancet</i> 2003; 361:1149-58	In hypertensive patients with risk factors for CHD and average or below-average cholesterol, atorvastatin reduced nonfatal MI, fatal CHD, fatal/nonfatal stroke, coronary events but not all-cause mortality
CAPRIE	<i>Lancet</i> 1996; 348:1329-39	In atherosclerotic vascular disease clopidogrel reduced the primary combined endpoint of stroke, MI or vascular death and improved PAD compared to ASA
CARE	<i>NEJM</i> 1996; 335:1001-9	Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol
CURE	<i>NEJM</i> 2001; 345:494-502	Clopidogrel plus ASA reduced death from CV causes, non fatal MI, or stroke but increased bleeding complications
EUROPA	<i>Lancet</i> 2003; 362:782-88	With stable CAD and no CHF perindopril reduced cardiovascular death, MI, and total mortality
HOPE	<i>NEJM</i> 2000; 342:154-60	In high-risk patients without low LVEF or CHF ramipril reduced rates of death, MI, stroke, revascularization, new diagnosis of diabetes and complications due to diabetes. Vitamin E had no effect on outcomes
HPS	<i>Lancet</i> 2002; 360:7-22	In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths and major vascular events
JUPITER	<i>NEJM</i> 2008; 359:2195-2207	With low to normal LDL-C and elevated hsCRP treatment with rosuvastatin significantly reduced major cardiovascular events. NNT with rosuvastatin for 2 yr to prevent one primary endpoint = 95
SYNTAX	<i>NEJM</i> 2009; 360:961-972	CABG has lower rate of major cardiac or cerebrovascular events. The rate of stroke was increased with CABG, whereas the rate of repeat revascularization was increased with PCI
TNT	<i>NEJM</i> 2005; 352:1425-35	Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d
WHI	<i>JAMA</i> 2002; 288:321-333	Estrogen plus progestin therapy is associated with increased risks of cardiovascular disease and breast cancer but decreased risks of hip fracture and colorectal cancer in postmenopausal women
<b>MYOCARDIAL INFARCTION</b>		
BHAT	<i>JAMA</i> 1982; 247:1707-14	In acute MI propranolol reduced all-cause mortality, cardiovascular death and sudden death from atherosclerotic heart disease
COURAGE	<i>NEJM</i> 2007; 356:1503-16	Compared with optimal medical therapy alone PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events
ISIS-2	<i>Lancet</i> 1988; 2:349-60	Early therapy with SK and ASA in patients with MI individually and in combination significantly reduced all-cause mortality and in combination demonstrated additive effect
ISIS-4	<i>Lancet</i> 1995; 345:669-85	In patients with suspected or definite acute MI early treatment with captopril reduced all-cause mortality at 35 d and during long-term follow up
OASIS-5	<i>NEJM</i> 2006; 354:1464-76	Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 and MI at 30 and 180 d
PROVE IT – TIMI 22	<i>NEJM</i> 2004; 350:1495-1504	In patients hospitalized for ACS high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin



Useful app “CHF Trials” available on iTunes®.

Trial	Reference	Results
<b>HEART FAILURE</b>		
AIRE	<i>Lancet</i> 1993; 342:821-8	Ramipril commenced 3-10 d after MI and continued for a mean 15-month period significantly reduced all-cause mortality in patients with non-severe CHF
CHARM	<i>Lancet</i> 2003; 362:759-66	Candesartan reduced overall mortality, cardiovascular death and CHF hospitalizations
CIBIS II	<i>Lancet</i> 1999; 353:9-13	Bisoprolol reduced all-cause mortality, cardiovascular death, all-cause hospitalization, and CHF hospitalization
COMET	<i>Lancet</i> 2003; 362:7-13	Carvedilol was associated with a reduction in all cause mortality compared with metoprolol
CONSENSUS	<i>NEJM</i> 1987; 316:1429-35	Enalapril reduced all-cause mortality, death due to progression of heart failure
COPERNICUS	<i>NEJM</i> 2001; 344:1651-8	Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF
I-PRESERVE	<i>NEJM</i> 2008; 359:2456-2467	In patients with CHF and normal LVEF treatment with ARB (irbesartan) did not improve mortality or cardiovascular morbidity compared to placebo
MERIT-HF	<i>Lancet</i> 1999; 353:2001-7	Metoprolol CR/XL daily in addition to optimum standard therapy improved survival in clinically stable patients equating to prevention of 1 death per 27 patients treated per year
RALES	<i>NEJM</i> 1999; 341:709-17	In severe CHF (class III/IV) and LVEF <35% spironolactone reduced all-cause mortality, sudden death, and death due to progression of heart failure
SAVE	<i>NEJM</i> 1992; 327:669-77	Patients with LV dysfunction post-MI long-term captopril over 3.5 yr reduced the risk of death due to cardiovascular causes, recurrent MI, development of severe CHF, and CHF hospitalization
SCD-HeFT	<i>NEJM</i> 2005; 352:225-237	In mild-to-moderate CHF shock-only ICD significantly reduces risk of death. Amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF
SOLVD	<i>NEJM</i> 1991; 325:293-302	In stable chronic CHF with decreased LVEF (<0.35) long-term enalapril reduced death due to all causes and death or hospitalization due to CHF
TRACE	<i>NEJM</i> 1995; 333:1670-6	In patients with LV dysfunction post-MI long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death
V-HeFT II	<i>NEJM</i> 1991; 325:303-10	In chronic CHF enalapril reduced mortality more than hydralazine-isosorbide for at least 2 yr. Treatment with either enalapril or hydralazine-isosorbide increased LVEF
<b>DIABETES</b>		
CARDS	<i>Lancet</i> 2004; 264:685-96	Atorvastatin reduces the risk of cardiovascular events in patients with type 2 DM
ONTARGET	<i>NEJM</i> 2008; 358:1547-59	In patients with vascular disease or DM without CHF telmisartan is equally as effective as ramipril, with telmisartan causing a reduced risk of cough and angioedema, and an increased risk of hypotensive symptoms. Combination therapy offers no advantage
<b>ARRHYTHMIA</b>		
AFFIRM	<i>NEJM</i> 2002; 347:1825-33	No significant difference in mortality rates between rate or rhythm control of AFib
AF-CHF	<i>NEJM</i> 2008; 358:2667-77	In patients with atrial fibrillation and congestive heart failure there is no significant difference in mortality rates from cardiovascular causes between rate and rhythm control
ROCKET-AF	<i>NEJM</i> 2011; 365:883-891	In patients with atrial fibrillation rivoxabarin in non-inferior to warfarin for stroke prevention, and major and non-major bleeding.
<b>HYPERTENSION</b>		
HYVET	<i>NEJM</i> 2008; 358:1887-98	In hypertensive patients >80 yr treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non fatal stroke
UKHDS (UKPDS)	<i>BMJ</i> 1998; 317:703-13	Hypertensive patients with DM and tight BP control at <150/85 mmHg by use of ACEI or $\beta$ -blocker reduced risk of diabetic complications and death related to DM and reduced risk of end-organ damage
VALUE	<i>Lancet</i> 2004; 363:2022-2031	Valsartan group had higher incidence of MI than amlodipine group, whereas amlodipine had a higher incidence of new onset diabetes

## References

### Ischemic Heart Disease

- Cannon CP, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *NEJM* 2004;350:1495-504.
- Lindahl B, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. *NEJM* 2000;343:1139-1147.
- Pitt B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *NEJM* 2003;348:1309-1321.
- Rauch U, et al. Thrombus formation on the atherosclerotic plaques: pathogenesis and clinical consequences. *Ann Intern Med* 2001;134:224-238.
- The Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *NEJM* 2001;344:1117-1124.
- Turpie AGG, Antman EM. Low-molecular-weight heparins in the treatment of acute coronary syndromes. *Arch Intern Med* 2001;161:1484-1490.
- Yeghiazarians Y, Braunstein JB, Askari A, Stone PH. Review article: unstable angina pectoris. *NEJM* 2000;342:101-114.

### Nuclear Cardiology

- Lee TH, Boucher CA. Noninvasive tests in patients with stable coronary artery disease (review). *NEJM* 2000;344:1840-1845.

### Cardiomyopathies

- Feldman AM, McNamara D. Myocarditis (review). *NEJM* 2000;343:1388-1398.

### Guidelines

- ACC/AHA guidelines for percutaneous coronary intervention. *Circulation* 2001;103:3019-3041.
- ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. Available at: <http://www.acc.org>.
- ACCF/AHA 2009 focused update on the guidelines for the diagnosis and management of heart failure in adults. *Circulation* 2009;119:1977-2016.
- ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;110:e82-292.
- American College of Cardiology (clinical guidelines, etc). Available from: <http://www.acc.org>.
- Antman EM, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – summary: a report of the American College of Canadian Cardiovascular Society (CCS) mobile guidelines. Available from: <http://www.ccs.ca/mobile.Free>.
- Aurigemma GP, et al. Clinical practice, diastolic heart failure. *NEJM* 2004;351:1097.
- Beard JD. Chronic lower limb ischemia. *BMJ* 2000;320:854-857.
- Canadian Cardiovascular Society 2005 Consensus Conference Peripheral Arterial Disease (Draft). Available from: <http://www.ccs.ca>.
- Cardiology. American Heart Association Task Force on practice guidelines. *Circulation* 2004;110:588.
- Cardiology Online (requires registration). Available from: <http://www.theheart.org>.
- CCS focused 2012 update of the CCS atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* 2012;28:125-136.
- CCS. The use of antiplatelet therapy in the outpatient setting: CCS guidelines. *Can J Cardiol* 2011;27:S1-S59.
- CCS. Working group: providing a perspective on the 2007 focused update of the ACC/AHA 2004 guidelines for the management of ST elevation myocardial infarction. *Can J Cardiol* 2009; 25:25-32.
- CCS. 2012 heart failure management guidelines update: Focus on acute and chronic heart failure. *Can J Cardiol* 2013;29:168-181.
- CCS. 2001 Canadian cardiovascular society consensus guideline update for the management and prevention of heart failure. *Can J Cardiol* 2001;17(supplE):5-24.
- Fuchs JA. ESO, et al. ESC guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries.
- Harrington RA, et al. Antithrombotic therapy for coronary artery disease: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126(3 suppl):513s-584s.
- Heart valve repair (internet). Available from: <http://www.heartvalverepair.net>.
- May J, White GH, Harris JP. The complications and downside of endovascular therapies. *Adv Surg* 2001;35:153-172.
- Rutherford RB. Vascular Surgery, 4th ed. Toronto: WB Saunders, 1995. Chapter: Atherogenesis and the medical management of atherosclerosis. p222-234.
- Schmieder FA, Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Card* 2001;87(Suppl):3D-13D.
- Simpson C, et al. CCS Consensus conference 2003: assessment of the cardiac patient for fitness to drive and fly: executive summary. *Can J Cardiol* 2004;20:1313-1323.
- Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2851-2906.
- Thygesen K, et al. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551-2567.
- Way LW, Doherty GM, editors. Current surgical diagnosis and treatment, 11th ed. Lange Medical Books/McGraw-Hill, 2004.
- Yang SC, Cameron DE, editors. Current therapy in thoracic and cardiovascular medicine. McGraw-Hill, 2004.

### Ambulatory ECG

- Zimetbaum, P, Josephson, M. The evolving role of ambulatory arrhythmia monitoring in general clinical practice. *Ann Intern Med* 1999;130:848-856.
- Kadish AH, Buxton AE, Kennedy HL. ACC/AHA clinical competence statement on electrocardiography and ambulatory electrocardiography: a report of the ACC/AHA/ACP-ASIM task force on clinical competence. *Circulation* 2001;104:3169-3178.
- Krahn A, Klein G, Skanes A, Yee R. Insertable loop recorder use for detection of intermittent arrhythmias. *Pacing and Clinical Electrophysiol* 2004;27:657-664.

### Stress Testing

- Allison T, Bardsley W, Behrenbeck T, et al. Mayo foundation for medical education and research. 1996;71:43-52.
- Gibbons, et al. Exercise testing guidelines. *JACC* 1997;30:260-315.

### Echocardiography

- Picano, E. Stress echocardiography: a historical perspective. *AJM* 2003;114:126-130.
- Heatlie G, Giles M. Echocardiography and the general physician. *Postgrad Med J* 2004;80:84-88.
- Cheitlin M. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article. *J Am Soc Echocardiography* 2003;16:1091-1110.
- Gowda R, Khan I, Sacchi T, Patel R. History of the evolution of echocardiography. *Int J Cardiol* 2004;97:1-6.

### Nuclear Cardiology

- Sabharwal N, Lahiri A. Role of myocardial perfusion imaging for risk stratification in suspected or known coronary artery disease. *Heart* 2003;89:1291-1297.
- Beller G, Zaret B. Contributions of nuclear cardiology to diagnosis and prognosis of patients with coronary artery disease. *Circulation* 2000;101:1465-1478.

### MR

- Kim WY, et al. Coronary magnetic resonance angiography for the detection of coronary stenoses. *NEJM* 2001;345:1863-1869.
- Danias P, Roussakis A, Ioannidis J. Cardiac imaging diagnostic performance of coronary magnetic resonance angiography as compared against conventional x-ray angiography: a meta-analysis. *J Am Col Cardiol* 2004;44:1867-1876.

### CT

- Miller JM, et al. Diagnostic performance of coronary angiography by 64-row CT. *NEJM* 2008;359:2324-2336.
- Schoepf J, Becker C, Ohnesorge B, Yucel K. CT of coronary artery disease. *Radiology* 2004;232:18-37.
- Somberg J. Arrhythmia therapy. *Am J Therapeutics* 2002;9:537-542.

**Cath/EPs**

- Hayes D, Furman S. Cardiac pacing: how it started, where we are, where we are going. *J Cardiovasc Electrophysiology* 2004;15:619-627.
- Zipes, et al. ACC/AHA task force report guidelines for clinical intracardiac electrophysiological and catheter ablation procedures. *JACC* 1995;26:555-573.
- Wellens J. Cardiac arrhythmias: the quest for a cure. *J Am Coll Cardiol* 2004;44:1155-1163.
- Conti J. ACC 2005 Annual session highlight. Cardiac arrhythmias. *J Am Coll Cardiol* 2005;45:B30-B32.
- Keane D. New catheter ablation techniques for the treatment of cardiac arrhythmias. *Card Electrophysiol Rev* 2002;6:341-348.
- Skanes A, Klein G, Kohn A, Yee R. Cryoablation: potentials and pitfalls. *J Cardiovasc Electrophysiol* 2004;15:528-534.
- Packer D. Evolution of mapping and anatomic imaging of cardiac arrhythmias. *J Cardio Electrophysiol* 2004;15:839-854.
- Zipes D. The year in electrophysiology. *J Am Coll Cardiol* 2004;43:1306-1324.
- Ryan TJ, Faxon DP, Gunnar RM, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on assessment of diagnostic and therapeutic cardiovascular procedures (subcommittee on percutaneous transluminal coronary angioplasty). *Circulation* 1988;78:486-502.

**Arrhythmias**

- Bernstein AD. The NASPE/BPEG pacemaker code. *Tex Heart Inst J* 1991;18:299-300.
- Camm AJ, Kirchhof P, Lip GYH, et al. Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Guidelines for the management of atrial fibrillation. *Eur Heart J* 2010;31:2369-2429.
- Gutierrez C, Blanchard DG. Atrial fibrillation: diagnosis and treatment. *Am Fam Phys* 2011;83:61-68.
- Garcia TB, Miller GT. Arrhythmia Recognition: The Art of Interpretation. Sudbury: Jones & Bartlett, 2004.
- Joep Thijssen, et al., Driving restrictions after implantable cardioverter defibrillator implantation: an evidence-based approach. *Eur Heart J* 2011;32:2678-2687.
- Lip GYH, Nieuwlaet R, Pisters R, Lane DR, Crijs HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro heart survey on atrial fibrillation. *Chest* 2010;137:263-72.
- Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *NEJM* 2011;365:883-891.
- Prystowsky EN, Topol EJ, Califf RM, Prystowsky EN, Thomas JD, Thompson PD (editors). Textbook of cardiovascular medicine, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2007. Chapter: Electrophysiology and pacing

**Percutaneous Angiography/PCI**

- Guidelines for percutaneous transluminal coronary angioplasty: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures Subcommittee on percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1988;12:529-545.
- O'Neil W, Dixon S, Grines C. The year in interventional cardiology. *J Am Coll Cardiol* 2005;45:1117-1134.
- Bashore, et al. ACC/SCAI expert consensus document. American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on Cardiac Catheterization Laboratory Standards. *J Am Coll Cardiol* 2001;37:2170-214.
- Baim D. New devices for percutaneous coronary intervention are rapidly making bypass surgery obsolete. *Curr Opin Cardiol* 2004;19: 593-597.
- Serruys PW, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *NEJM* 2009;360:961-972.

**Cardiovascular Surgery**

- Alexander P, Giangola G. Deep venous thrombosis and pulmonary embolism: diagnosis, prophylaxis, and treatment. *Ann Vasc Surg* 1999;13:318-327.
- American College of Cardiology (clinical guidelines, etc). Available from: <http://www.acc.org>.
- Beard JD. Chronic lower limb ischemia. *BMJ* 2000;320:854-857.
- Bojar RM. Manual of perioperative care in cardiac surgery, 3rd ed. Massachusetts: Blackwell Science, 1999.
- Cardiology Online (requires registration). Available from: <http://www.theheart.org>.
- Cheng DCH, David TE. Perioperative care in cardiac anesthesia and surgery. Austin: Landes Bioscience, 1999.
- Coulam CH, Rubin GD. Acute aortic abnormalities. *Semin Roentgenol* 2001;36:148-164.
- Crawford ES, Crawford JL, Veith FJ, Hobson RW, Williams RA, and Wilson SE (editors). Vascular surgery: principles and practice, 2nd ed. Toronto: McGraw-Hill, 1994. Chapter: Thoracoabdominal aortic aneurysm.
- Fuchs JA, Rutherford RB (editors). Vascular Surgery, 4th ed. Toronto: WB Saunders, 1995. Chapter: Atherogenesis and the medical management of atherosclerosis. p222-234.
- Freischlag JA, Veith FJ, Hobson RW, Williams RA, and Wilson SE (editors). Vascular surgery: principles and practice, 2nd ed. Toronto: McGraw-Hill, 1994. Chapter: Abdominal aortic aneurysms.
- Hallett JW Jr. Abdominal aortic aneurysm: natural history and treatment. *Heart Dis Stroke* 1992;1:303-308.
- Hallett JW Jr. Management of abdominal aortic aneurysms. *Mayo Clin Proc* 2000;75:395-399.
- Harlan BJ, Starr A, Harwin FM. Illustrated handbook of cardiac surgery. New York: Springer-Verlag, 1996.
- Heart Valve Repair (internet). Available from: <http://www.heartvalverepair.net>.
- Hiratzka LF, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol* 2010;55:e27-e129.
- May J, White GH, Harris JP. The complications and downside of endovascular therapies. *Adv Surg* 2001;35:153-35172.
- Pitt MPI, Bonser RS. The natural history of thoracic aortic aneurysm disease: an overview. *J Card Surg* 1997;12(Suppl):270-278.
- Powell JT, Brown LC. The natural history of abdominal aortic aneurysms and their risk of rupture. *Adv Surg* 2001;35:173-185.
- Rabi, D, et al. Effect of perioperative glucose-insulin-potassium infusions on mortality and atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. *Can J Cardiol* 2010;26;178-184.
- Rosen CL, Tracy JA. The diagnosis of lower extremity deep venous thrombosis. *Em Med Clin N Am* 2001;19:895-912.
- Schmieder FA, Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Am J Card* 2001;87(Suppl):3D-13D.
- Verma S, Szmikto PE, et al. Clinician update: should radial arteries be used routinely for coronary artery bypass grafting? *Circulation* 2004;110:e40-e46.
- Way LW, Doherty GM. Current surgical diagnosis and treatment, 11th ed. Lange Medical Books/McGraw-Hill, 2004.
- Yang SC, Cameron DE. Current therapy in thoracic and cardiovascular medicine. McGraw-Hill, 2004.

Rick Chen, Erica Merman and Monique Moller, chapter editors

Maria Jogova and Howard Meng, associate editors

Melini Gupta, EBM editor

Dr. David Juurlink, staff editor

<b>General Principles</b> . . . . .	<b>2</b>	<b>Pharmacodynamics</b> . . . . .	<b>7</b>
Drug Nomenclature		Dose-Response Relationship	
Phases of Clinical Testing		Efficacy	
Drug Administration		Potency	
<b>Pharmacokinetics (ADME)</b> . . . . .	<b>3</b>	Effects of Drugs on Receptors	
Absorption		Agonists	
Mechanisms of Drug Absorption		Antagonists	
Factors Affecting the Rate and Extent of Drug Absorption		Effectiveness and Safety	
Bioavailability		Therapeutic Indices	
First-Pass Effect			
Efflux Pump		<b>Therapeutic Drug Monitoring (TDM)</b> . . . . .	<b>9</b>
Distribution		<b>Adverse Drug Reactions (ADRs)</b> . . . . .	<b>10</b>
Factors Affecting the Rate and Extent of Drug Distribution		Type A Drug Reactions	
Volume of Distribution		Type B Drug Reactions	
Plasma Protein Binding		Type C Drug Reactions	
Depots		Type D Drug Reactions	
Barriers		Other ADR Categories	
Metabolism (Biotransformation)		Approach to Suspected ADRs	
Drug Metabolizing Pathways		<b>Variability in Drug Response</b> . . . . .	<b>11</b>
Factors Affecting Drug Biotransformation		<b>Drug Interactions</b> . . . . .	<b>12</b>
Elimination		<b>Autonomic Pharmacology</b> . . . . .	<b>12</b>
Routes of Drug Elimination		Parasympathetic Nervous System (PNS)	
Pharmacokinetic Calculation		Sympathetic Nervous System (SNS)	
Time-Course of Drug Action		<b>Common Drug Endings</b> . . . . .	<b>14</b>
Half-Life		<b>References</b> . . . . .	<b>14</b>
Steady State			
Clearance			
Elimination Kinetics			

## Acronyms

ACh	acetylcholine	F	bioavailability	P <sub>o/w</sub>	partition coefficient of a drug
ADR	adverse drug reaction	GFR	glomerular filtration rate	Pgp	p-glycoprotein
BBB	blood brain barrier	NE	norepinephrine	TI	therapeutic index
Cl	clearance	PD	pharmacodynamics	Vd	volume of distribution
CYP	cytochrome P450 protein	PK	pharmacokinetics		

# General Principles

## Drug Nomenclature

- **chemical name:** describes chemical structure; same in all countries
  - e.g. *N*-(4-hydroxyphenyl)acetamide is acetaminophen
- **drug identification number (DIN) or national drug code (NDC):** DIN assigned by Health Canada; NDC assigned by FDA (US)
- **non-proprietary name:** approved name (post-phase III trial), official name (listed in pharmacopoeia), or generic name (off-patent)
  - e.g. acetaminophen
- **proprietary (trade) name:** the brand name or registered trademark
  - e.g. Tylenol®
- **street name:** slang term used for a drug of abuse

## Phases of Clinical Testing

- **phase I:** first administration to healthy human volunteers, following animal studies; to determine PK and PD
- **phase II:** first administration to patients, small sample sizes; to determine initial safety and effectiveness, dose range, PK, PD
- **phase III:** large sample sizes, often double-blind RCT; comparative (new drug vs. placebo or standard of care) to establish safety and efficacy
- **phase IV:** post-marketing surveillance, wide distribution; to determine rare adverse reactions, effects of long-term use, ideal dosing, effects in real world practice



At the time of drug launch, only data from phases I-III are available; thus true effectiveness (in contrast to efficacy) and safety may be unknown because real-world patients and usage patterns sometimes differ significantly from those in premarket phases.

## Drug Administration

- choice of route of administration depends on
  - drug properties
  - local and systemic effects (limiting action or adverse events)
  - desired onset and/or duration of action
  - patient characteristics

Table 1. Routes of Drug Administration

Route	Advantage	Disadvantage
<b>Oral (PO)</b>	Convenient, easy to administer Large surface area for absorption Inexpensive relative to parenteral administration	Drug metabolism by GI secretions Incomplete absorption Hepatic first-pass effect Potential GI irritation
<b>Buccal/Sublingual (SL)</b>	Rapid onset of action No hepatic first-pass effect	Must be lipid-soluble, non-irritating Short duration of action
<b>Rectal (PR)</b>	Almost no hepatic first-pass effect Convenient if NPO, vomiting or unconscious	Inconvenient, irritation at site of application Erratic absorption
<b>Intravenous (IV)</b>	Direct to systemic circulation No hepatic first-pass effect Slow infusion or rapid onset of action Easy to titrate dose	Requires IV access, aseptic technique Hard to remove once administered Risk of infection, bleeding, vascular injury, extravasation Expensive
<b>Intra-arterial</b>	Direct to specific organs (heart, brain) No hepatic first-pass effect	Risk of infection, bleeding, vascular complications
<b>Intramuscular (IM)</b>	Depot storage if oil-based = slow release of drug Aqueous solution = rapid onset of action	Pain at site of injection



### Common Latin Abbreviations

q	each, every
OD/bid/tid/qid	once/twice/three/four times a day
hs	at bedtime
ac/pc/cc	before/after/with meals
prn	as necessary
gtt	drops
ung	ointment
ud	as directed
od/os/ou	right/left/each eye
ad/as/au	right/left/each ear



**Table 1. Routes of Drug Administration** (continued)

Route	Advantage	Disadvantage
<b>Subcutaneous (SC)</b>	Non-irritating drugs, small volumes Constant, even absorption Alternative to IV	Pain at site of injection Smaller volumes than IM May have tissue damage from multiple injections
<b>Intrathecal</b>	Direct into cerebrospinal fluid (CSF) Bypass BBB and blood-CSF barrier	Risk of infection Possibility of brain herniation and coning
<b>Inhalation</b>	Immediate (local) action in lungs Rapid delivery to blood (systemic action) No hepatic first-pass effect	Must be a gas, vapour or aerosol
<b>Topical</b>	Easy to administer Localized (limited systemic absorption)	Effects are mainly limited to site of application
<b>Transdermal</b>	Drug absorption through intact skin No hepatic first-pass effect	Irritation at site of application Delayed onset of action Hydrophilic drugs are not easily absorbed
<b>Others (intraperitoneal, intra-articular)</b>	Local effect	Risk of infection

## Pharmacokinetics (PK)

- study of “what the body does to a drug”
- definition: relationship between drug administration, time-course/rate of distribution, concentrational changes in the body compartments, and the drug's removal from the body

## Absorption

- definition: movement of the drug from the site of administration into plasma

### Mechanisms of Drug Absorption

- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms: active transport, facilitated diffusion, pinocytosis/phagocytosis

### Factors Affecting the Rate and Extent of Drug Absorption

- **partition coefficient** of a drug ( $P_{o/w}$ ), i.e. its relative solubility in oil (lipid) vs. water
- **local blood flow** at the site of administration (e.g. sublingual vessels facilitate rapid absorption from SL)
- **molecular size** (e.g. small molecular weight drugs absorb faster)
- **pH and drug ionization**
  - drugs are usually weak acids (e.g. acetylsalicylic acid) or weak bases (e.g. ketoconazole) and thus have both ionized and non-ionized forms
  - body compartment pH and drug  $pK_a$  determine the ratio of ionized:non-ionized ratio (using the Henderson-Hasselbach equation)
  - non-ionized forms cross cell membranes much faster than ionized (charged) forms
- **total surface area for absorption**
  - small intestinal villi (large surface area) is the primary site of absorption for most oral drugs

### Bioavailability (F)

- definition: fraction of dose after administration that reaches systemic circulation in an unchanged state
- affected by: drug absorption, gut metabolism, and hepatic first-pass effect
- IV dose has 100% bioavailability ( $F = 1$ )
- drugs with a low bioavailability by PO may require a much larger oral dose when compared to the IV dose (e.g.  $\beta$ -blockers: metoprolol 5 mg IV vs. metoprolol 50 mg PO)

### First-Pass Effect

- definition: drug metabolism by the liver and sometimes the gut before it reaches systemic circulation, resulting in reduced drug bioavailability
- occurs with PO administration of a drug: GI tract (absorption) → portal vein to liver (first-pass metabolism) → systemic circulation
- occurs to much lesser extent with PR administration because drug absorbed in colon bypasses the portal system: colon (absorption) → internal pudendal veins → IVC → systemic circulation



#### Partition Coefficient ( $P_{o/w}$ )

- Ratio of a drug's solubility in oil/lipid (e.g. cell membrane) as compared to water (e.g. extracellular fluid)
- A large  $P_{o/w}$  (e.g. anesthetics) means that a drug is highly soluble in lipid and will cross membranes easily



#### Drug Ionization Reaction and the Henderson-Hasselbach Equation

for a weak acid:

$HA \rightleftharpoons A^- + H^+$ ;  $pK_a = pH + \log [HA/A^-]$   
e.g. drug  $pK_a = 4.4$  at a gastric pH of 1.4,  
non-ionized:ionized =  $HA:A^- = 1:0.001$   
Thus, weak acids are mainly non-ionized and more readily absorbed in stomach.

for a weak base:

$BH^+ \rightleftharpoons B + H^+$ ;  $pK_a = pH + \log [BH^+/B]$   
Weak bases more readily absorbed in small intestine (pH ~6.0-9.0)



#### Examples of Drugs with High First Pass Effect (Hepatic Extraction)

- Levodopa
- Morphine
- Propranolol
- Lidocaine
- Organic nitrates



#### Examples of Drugs with Low First Pass Effect

- Diazepam
- Digoxin
- Phenytoin
- Warfarin

### Efflux Pump

- P-glycoprotein (Pgp) is a protein in the GI tract, renal epithelium, and elsewhere that acts as a multidrug efflux pump involved in the transport of drugs out of cells
- acts to reduce intestinal absorption and enhance renal elimination of certain drugs, e.g. digoxin, dabigatran, etexilate, etoposide, paclitaxel, tacrolimus, cyclosporine
- some drugs (e.g. macrolide antibiotics) inhibit Pgp function, leading to increased levels of Pgp substrates. Pgp inducers (e.g. St. John's Wort) do the opposite
- some tumours overexpress Pgp leading to multi-drug resistance to chemotherapy agents

## Distribution

- definition: movement of drugs between different body compartments and to the site of action
- major body fluid compartments: plasma, interstitial fluid, intracellular fluid, transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments: fat, brain

### Factors Affecting the Rate and Extent of Drug Distribution

- physiochemical properties of the drug (e.g. partition coefficient)
- pH of fluid
- plasma protein binding
- binding within compartments (depots, e.g. % body fat)
- cardiac output
- regional blood flow

### Volume of Distribution ( $V_d$ )

- maximum actual  $V_d$  (anatomic fluid volume accessible to drug) = total body water (TBW ~40 L for average adult) (see Figure 1)
- $V_d$ : the apparent volume of fluid into which a drug dissolves
  - a calculated value = amount of drug in body ÷ plasma drug concentration
  - a theoretical value that does not correspond to an anatomical space (can exceed TBW)
  - the value takes into account drug distribution into tissues and protein binding
  - small  $V_d$  corresponds to a drug which concentrates in plasma and/or binds plasma proteins to a high degree
  - large  $V_d$  corresponds to a drug which distributes into tissues; most is not in blood (measured) space, and it therefore "appears" to distribute in a large volume
  - volume of distribution of plasma-protein bound drugs can be altered by liver and kidney disease
- example: amiodarone distributes into TBW (actual  $V_d$  = 40 L), but it also concentrates in fat tissues giving instead an apparent  $V_d$  of 400 L; i.e. to achieve a given plasma concentration of amiodarone, we dose as though the drug distributes into 400 L of body fluid

### Plasma Protein Binding

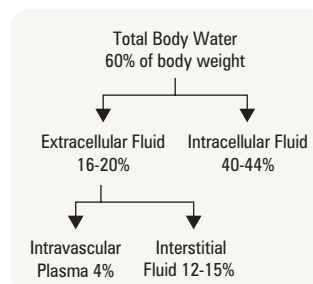
- drug molecules in the blood exist in an equilibrium of two forms:
  1. bound to plasma proteins
    - ♦ acidic drugs bind to albumin
    - ♦ basic drugs bind to  $\alpha_1$ -acid glycoprotein
  2. free or unbound
    - ♦ can leave the circulation to distribute into tissues and exert an effect; subject to metabolism and elimination
- bound fraction is determined by
  - drug concentration, binding affinity, and plasma protein concentration (# of binding sites)
- reduced # of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in an increase in free drug concentration, potentially leading to toxicity (see sidebar). However, more commonly most free drug will be metabolized and toxicity will not be seen

### Depots

- a body compartment where drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wks)

### Barriers (relative)

- body structures that limit or prevent diffusion of drug molecules
  - e.g. the placenta or blood brain barrier (BBB – a barrier composed of tight junctions between capillary endothelial cells and astrocytes)



**Figure 1. Distribution of total body water (TBW)**



Special consideration must be given in dosing patients in **hypoalbuminemic** states (liver failure or nephrotic syndrome) to prevent drug toxicity. Highly protein-bound drugs (e.g. warfarin, digoxin, diazepam, furosemide, amitriptyline) will exert a greater effect in these patients than in healthy individuals because of higher levels of free drug.



Multiple drugs and endogenous substances can **compete** for the same protein binding sites, e.g. ASA displaces highly protein-bound acidic drugs such as phenytoin, thus increasing risk of toxicity; sulfonamide displaces bilirubin, which could potentially lead to jaundice and kernicterus in neonates.



### Main Factors Governing Penetration of Blood Brain Barrier (BBB)

- Small molecular size (<500 Daltons)
- High lipid solubility
- Active transport mechanisms (e.g. Pgp multidrug efflux pump)

### Many Drugs Cross BBB:

- General anesthetics
- Alcohol
- Nicotine
- Caffeine
- L-dopa
- Opioids
- Psychotropic medications

- many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. Pgp) which serve as a natural defense mechanism against drugs and xenobiotics
- need to consider dosing route if drugs are meant to cross these barriers

## Metabolism (Biotransformation)

- definition: chemical transformation of a drug *in vivo*
- sites of biotransformation: liver (main), GI tract, lung, plasma, kidney
- goal is to make compounds more hydrophilic to enhance renal elimination
- as a result of the process of biotransformation:
  - a pro-drug may be **activated** (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be **changed** to another active metabolite (e.g. diazepam to oxazepam)
  - a drug may be **changed** to a toxic metabolite (e.g. meperidine to normeperidine)
  - a drug may be **inactivated** (most drugs)

### Drug Metabolizing Pathways

- **phase I (P450) reactions**
  - small molecular changes introduce or unmask polar chemical groups on a parent compound to increase its water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation); the change in  $P_{o/w}$  is typically minimal compared to phase II, and often phase I places a polar 'handle' on a lipophilic drug to allow for phase II
  - mediated by cytochrome P450 enzymes found in the endoplasmic reticulum
  - product of the reaction can be excreted or undergo further phase II reactions
- **phase II (conjugation) reactions**
  - conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
  - dramatically increases water solubility and renal elimination
  - can occur independently of phase I reactions

### Factors Affecting Drug Biotransformation

- **genetic polymorphism** of metabolizing enzymes
  - individuals may metabolize drugs faster or slower depending on their genotype resulting in poor, intermediate, extensive or ultrarapid metabolizers
  - may lead to toxicity or ineffectiveness of a drug at a normal dose, e.g. tamoxifen and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas overactive/duplicated alleles impart "ultrarapid metabolizer" phenotype), while warfarin is metabolized by CYP2C9 (nonfunctional alleles lead to lower dose requirements)
- **enzyme inhibition** may sometimes be due to other drugs
  - P450 enzyme inhibition leads to an increased concentration and bioavailability of the substrate drug
  - e.g. erythromycin, ketoconazole, indinavir and grapefruit juice (CYP3A4 inhibitors) can predispose a patient to drug toxicity from other drugs also metabolized by CYP3A4 (e.g. simvastatin)
- **enzyme induction**
  - certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
  - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCP and bilirubin) by inducing the P450 enzyme system
- **liver dysfunction** (e.g. hepatitis, alcoholic liver, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but this may not be clinically significant due to the liver's reserve capacity
- **renal disease** often results in decreased drug clearance if it is renally cleared
- **extremes of age** (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
- **nutrition**
  - insufficient protein and fatty acid intake decrease P450 biotransformation
  - vitamin and mineral deficiencies may also impact metabolizing enzymes
- **alcohol**: while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1 and increase the risk of hepatocellular damage from acetaminophen by increasing the generation of acetaminophen's toxic metabolite
- **smoking** can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. smokers may require higher doses of theophylline, which is metabolized by CYP1A2)



#### Cytochrome P450 System

The P450 enzymes are a superfamily of heme proteins that are grouped into families and subfamilies according to their amino acid sequence. These proteins are responsible for the metabolism of drugs, chemicals and other substances.

Nomenclature: CYP3A4

"CYP" = cytochrome P450 protein

1st number = family

letter = subfamily

2nd number = isoform

The CYP1, CYP2, and CYP3 families metabolize most drugs in humans. The most important isoforms are CYP3A4 and CYP2D6; therefore, anticipate drug interactions if prescribing drugs using these enzymes.



#### Common Examples of P450 Inhibitors and Inducers

##### P450 inhibitors "MINCE"

Metronidazole (CYP 2C9)

Isoniazid (CYP 2C9), Indinavir (CYP 3A4)

Naringin or bergamottin (bioflavonoid in grapefruit) (CYP 3A4)

Ciprofloxacin (CYP 3A4, 1A2)

Erythromycin (macrolides) (CYP 3A4)

##### P450 inducers

Phenytoin (CYP 3A4)

Dexamethasone (CYP 3A4)

Phenobarbital (CYP 3A4)

Rifampin (CYP 2D6, 3A4)

Smoking (CYP 1A2)

St John's Wort (CYP3A4, CYP2C19, pgp)

Note: The above list is not exhaustive.



The **very** young and the **very** old are **very** sensitive to the actions of drugs.

## Elimination

- definition: removal of drug from the body

### Routes of Drug Elimination

- kidney** (main organ of elimination)
  - two mechanisms for **renal elimination**
    - glomerular filtration**
      - a passive process, so that only the free drug fraction can be filtered
      - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
    - tubular secretion**
      - an active process that is saturable, allowing both protein-bound and free drug fractions to be excreted
      - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
      - drugs may competitively block mutual secretion if both use the same secretion system (e.g. probenecid can be used to reduce the excretion of penicillin, thereby prolonging the half-life and thus the effect of the antibiotic)
  - tubular reabsorption**: drugs can be passively reabsorbed back to the systemic circulation, countering elimination mechanisms
  - renal function** (decreases with age and is affected by many disease states) is assessed clinically by using serum creatinine (Cr) levels
- stool**
  - some drugs and metabolites are actively excreted in the bile (e.g. corticosteroids) or directly into the intestinal tract from systemic circulation
  - enterohepatic reabsorption counteracts stool elimination, and thus can substantially prolong the drug's duration in the body
  - some glucuronic acid conjugates that are excreted in the bile will be hydrolyzed in the intestines by bacteria back to its original form that can be systemically reabsorbed
- lungs**
  - elimination of anesthetic gases and vapours by exhalation
- saliva**
  - saliva concentrations of some drugs parallel their plasma levels (e.g. rifampin)



Avoid toxicity from drug or metabolite accumulation by adjusting a drug's dosage according to the elimination characteristics of the patient (e.g. in renal impairment).



**The Cockcroft-Gault Equation can estimate creatinine clearance (CrCl) in adults 20 yr of age and older:**

For males  

$$\text{CrCl (mL/min)} = \frac{[(140 - \text{age in yr}) \times \text{Weight (kg)}] \times 1.2}{\text{serum Cr (}\mu\text{mol/L)}}$$

For females, multiply above equation x 0.85

Only applies when renal function is at steady state

## Pharmacokinetic Calculation

- definition: the quantitative description of the rates of the various steps of drug disposition (i.e. how drugs move through the body)
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism, and elimination) can be graphically represented on the concentration vs. time graph (see Figure 2)

### Time-Course of Drug Action

- many kinetic parameters are measured using IV dosing, such that absorption is immediate and distribution for most drugs is rapid; thus elimination is the main process being measured
- the concentration axis is converted to a  $\log_{10}$  concentration to allow for easier mathematical calculations (see Figure 3)

### Half-Life ( $t_{1/2}$ )

- definition: time taken for the serum drug level to fall 50% during elimination
- for drugs with first order kinetics: takes five half-lives to reach steady state with repeated dosing or for drug elimination once dosing is stopped
- see sidebar for calculation

# of Half Lives	1	2	3	3.3	4	5
Concentration	50%	75%	87.5%	90%	93.8%	96.9%

### Steady State

- drug concentration stays constant when the same amount of drug entering the system is eliminated from the system
- appropriate timing is important for therapeutic monitoring since drug levels are reliable only when the drug has reached steady state (see Figure 4)



### Principles of Pharmacokinetics

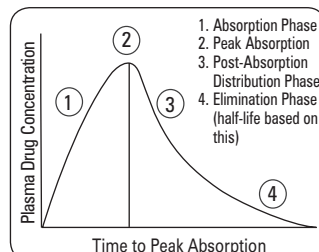
$V_d$  = amount of drug in the body/  
plasma drug concentration

Cl = rate of elimination of drug/plasma  
drug concentration

$$\text{Half-life (}t_{1/2}\text{)} = 0.7 \times V_d / \text{Cl}$$



For most drugs it takes 5 half-lives to reach steady state with repeated dosing or to eliminate a drug once dosing is stopped.



**Figure 2. Time course of drug action**

- special situations
  - use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
  - use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, insulin, unfractionated heparin)

### Clearance (Cl)

- a quantitative measurement of the body fluid volume from which a substance is removed per unit time
- $Cl = \text{rate of elimination of drug} \div \text{plasma drug concentration}$
- must consider clearance from a specific part of the body and total body clearance

### Elimination Kinetics (see Figure 5)

- first-order kinetics (most common type)
  - constant fraction of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the clearance decreases
  - becomes linear relationship when plotted on a log(concentration) vs. time graph (see Figure 3)
- zero-order kinetics (less common, associated with toxicities, e.g. alcohol)
  - a constant rate of drug eliminated regardless of concentration; concept of half-life does not apply

**Table 2. Loading vs. Maintenance Dosing**

Loading Dose	Maintenance Dose
Use when you need an IMMEDIATE effect	After a loading dose OR beginning with maintenance doses
Often parenteral medication	Steady-state levels achieved after ~5 half lives
Rationale: give large dose of medication to "fill up" the volume of distribution	Can be given as either a continuous infusion (relatively rare, short half-life drug) OR much more commonly as intermittent doses

## Pharmacodynamics (PD)

- study of "what a drug does to the body"

## Dose-Response Relationship

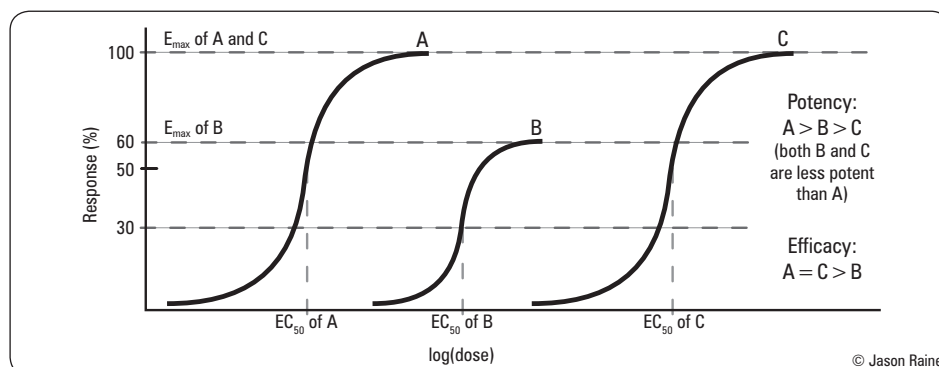
- graded dose-response relationships: the response of the drug reflects the number of receptors that are effectively occupied

### Efficacy

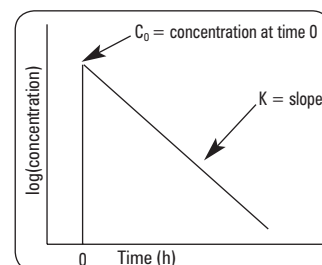
- measured as  $E_{\max}$  = the maximal response that a drug can elicit in an RCT or under optimal circumstances (see Figure 6)

### Potency

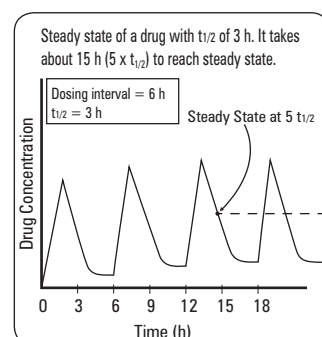
- measured as  $EC_{50}$  = the effective concentration of a drug needed to produce 50% of  $E_{\max}$  (see Figure 6)
- the drug that reaches its  $EC_{50}$  at the lower dose is the more potent
- overcome low potency by increasing the dose of the drug (e.g. 30 mg vs. 15 mg) to achieve desired response, provided that the higher dose not cause adverse effects



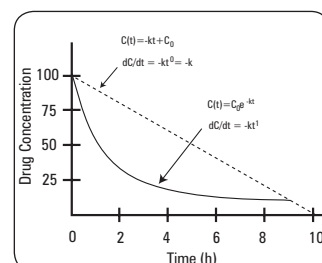
**Figure 6. log(dose)-response curve illustrating efficacy and potency**



**Figure 3. log(concentration) vs. time graph (IV bolus dose)**



**Figure 4. Steady state of a drug**



**Figure 5. First and zero order kinetics**

In first order kinetics (solid line), a constant fraction of the drug is eliminated per unit time; in zero order kinetics (dashed line), a constant amount of the drug is eliminated per unit time.



For unit conversion factors, please see Appendix: Common Unit Conversions.



### Efficacy versus Potency

- Efficacy measures the maximal effect of a drug
- Potency measures the concentration of a drug needed to produce a certain effect



## Effects of Drugs on Receptors

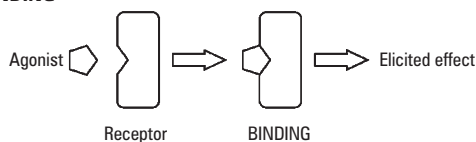
### Agonists

- drugs that mimic endogenous ligands and exert an effect
- have two main properties
  - **affinity**: the ability of the agonist to bind to the receptor (e.g. the  $\beta_2$ -agonist salbutamol has greater affinity for  $\beta_2$ -receptors than  $\beta_1$ -receptors)
  - **efficacy**: the ability to recapitulate endogenous response via the receptor interaction (e.g. binding of salbutamol to  $\beta_2$ -receptors results in smooth muscle relaxation)
- **full agonists**: can elicit a maximal effect at a receptor
- **partial agonists**: can only elicit a partial effect, no matter how high the concentration
  - e.g. reduced efficacy compared to full agonists

### Antagonists

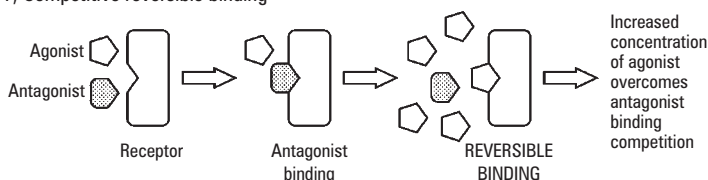
- drugs that have affinity (can bind to a receptor) but exert no effect
- these are drugs that block the action of an agonist or of an endogenous ligand
- **chemical antagonism**: direct chemical interaction between agonist and antagonist that prevents agonist binding to receptor
  - e.g. chelating agents for removal of heavy metals
- **functional antagonism**: two agonists that act independently at different receptors but have opposite physiological effects
  - e.g. acetylcholine at the muscarinic receptor decreases HR, constricts pupils, and stimulates intestinal motility; whereas epinephrine at the adrenergic receptor increases HR, dilates pupils, and decreases intestinal motility
- **reversible competitive antagonism** (most common in clinical practice, see Figure 8)
  - antagonist reversibly binds to the same receptor as the agonist, thus displacing it (e.g. naloxone is an antagonist to morphine or heroin)
- **irreversible antagonism** (see Figure 9)
  - antagonist irreversibly binds to the same receptor as the agonist, blocking it from binding (e.g. Phenoxybenzamine forms a permanent covalent bond with adrenergic receptors preventing adrenaline and noradrenaline from binding)
- **non-competitive antagonism** (see Figure 7)
  - antagonist binds to an alternate site separate but near the agonist site, producing allosteric effects that change the ability of the agonist to bind (e.g. organophosphates irreversibly bind acetylcholinesterase)

#### AGONIST BINDING

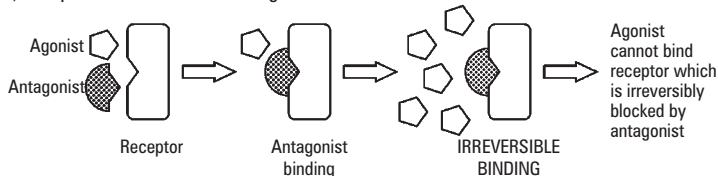


#### ANTAGONIST BINDING

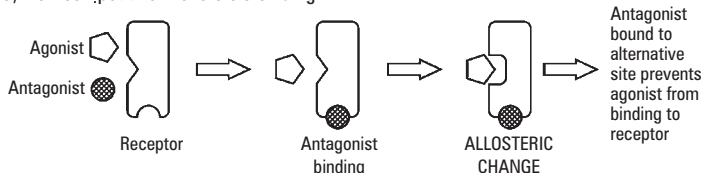
##### 1) Competitive reversible binding



##### 2) Competitive irreversible binding



##### 3) Non-competitive irreversible binding



© Adrian Yen 2006

Figure 7. Mechanism of agonists and antagonists

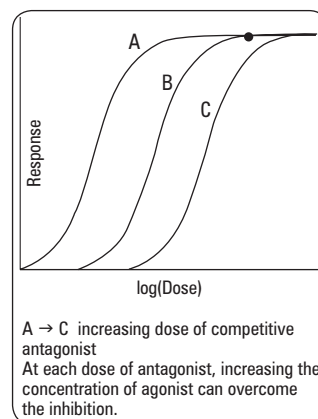


Figure 8. The log(dose)-response curve for competitive reversible antagonism

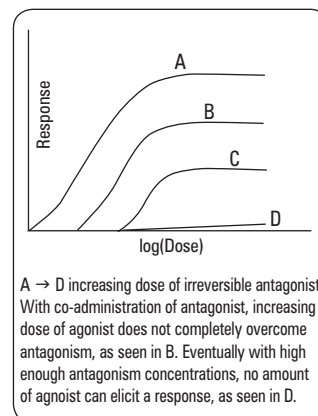


Figure 9. The log(dose)-response curve for irreversible antagonism



## Effectiveness and Safety

### Effectiveness

- $ED_{50}$  (Effective Dose – 50%): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

### Safety

- $LD_{50}$  (Lethal Dose – 50%): the dose of a drug needed to cause death in 50% of a test population of subjects (usually rodents)
- $TD_{50}$  (Toxic Dose – 50%): the dose needed to cause a harmful effect in 50% of a test population of subjects



The two most clinically relevant properties of any drug are effectiveness and safety.

## Therapeutic Indices

### Therapeutic Index (TI): $TD_{50}/ED_{50}$ (see Figure 10)

- reflects the “margin of safety” for a drug – the likelihood of a therapeutic dose causing serious toxicity or death
- the larger the TI, the safer a drug (e.g. warfarin has a narrow TI and requires accurate therapeutic monitoring)
- factors that can change the  $ED_{50}$ ,  $LD_{50}$  or  $TD_{50}$ 
  - presence of interacting drugs
  - changes in drug absorption, distribution, metabolism, elimination



Drugs with a narrow TI have a high likelihood of causing toxicity and need close therapeutic monitoring.

### Certain Safety Factor (CSF): $TD_1/ED_{99}$

- $CSF > 1$  translates to a dose effective in at least 99% of the population and toxic in less than 1% of the population.
- unlike TI, CSF does not take into account the shape of the cumulative dose-response curves of the therapeutic and toxic effects

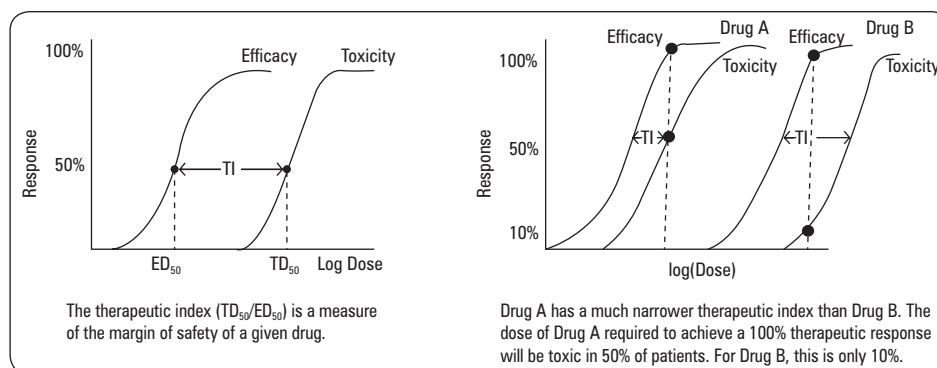


Figure 10.  $ED_{50}$ ,  $TD_{50}$ , and the therapeutic index (TI)

## Therapeutic Drug Monitoring (TDM)

- definition: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance)
  - serum drug samples are usually taken when the drug has reached steady state (e.g. trough level – the lowest level before the next dose)
- TDM can serve to monitor for side effects (e.g. vancomycin trough levels) and for desired effect (e.g. INR when on warfarin therapy)
- TDM is often used for drugs that have:
  - narrow therapeutic index (TI)
  - unpredictable dose-response relationship
  - significant consequences associated with therapeutic failure or toxicity
  - wide inter-patient pharmacokinetic variability



Examples of drugs whose levels need to be monitored: warfarin (via INR levels), digoxin, lithium, anti-epileptics (e.g. phenytoin, carbamazepine), and many others.

## Adverse Drug Reactions (ADRs)

**Table 3. Comparison of Characteristics of Type A and Type B Reactions**

Type A	Type B
Predictable extension of drug's pharmacologic effect	Unpredictable
Usually dose dependent	Rarely dose dependent
Low mortality (some exceptions)	High mortality (some exceptions)
Responds to dose reduction	Responds to drug withdrawal



In Canada, an estimated 1.6% of patients admitted to hospitals experience a serious adverse drug reaction. Furthermore, up to 24% of hospitalizations are drug related, of which 35.5% are adverse drug reactions.

### Type A Drug Reactions

- definition: undesirable normal/augmented responses to the drug (>80% of all ADRs)
- extension of a drug's pharmacological effects (e.g.  $\beta$ -blockers causing bradycardia; acetaminophen causing hepatitis)
- **overdose/toxicity**: exaggerated but characteristic pharmacological effect from supra-therapeutic dose
- **teratogen**: drug may produce developmental defects in fetus (not always in a dose-related manner)

### Type B Drug Reactions

- definition: reactions unrelated to the known pharmacological actions of the drug
- idiosyncratic: uncharacteristic response to drug, unrelated to pharmacology (e.g. sulfa-containing medications causing toxic epidermal necrolysis)
- **allergic/immune-mediated**: does not occur on first exposure (up to 7 d), immediate with subsequent exposure, may occur with low doses, often resolves within 3-4 d of discontinuation
- **pseudoallergic**: mimics immune-mediated reaction

### Type C Drug Reactions

- associated with long-term drug therapy
- effects are well-known and can be anticipated
- i.e. benzodiazepine dependence, analgesic nephropathy

### Type D Drug Reactions

- delayed effects
- carcinogenic or teratogenic

### Other ADR Categories

- type E (end-of-treatment effects)
- type F (failure of therapy)

### Approach to Suspected ADRs

- history and physical examination: signs and symptoms of the reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, dechallenge (response when drug is removed) and rechallenge (response when drug is given again)
- differentiate between drug therapy vs. disease pathophysiology
- treatment: stop the drug, supportive care, symptomatic relief
- resources: check recent literature, Health Canada and FDA; contact the pharmaceutical company; call Poison Control (1-888-268-9017) if overdose or poisoning suspected; check with Motherisk ([www.motherisk.org](http://www.motherisk.org)) in cases involving pregnant or breastfeeding women
- Canadian Adverse Drug Reaction Monitoring Program available online for reporting
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity

**Table 4. Sample of Clinically Relevant Adverse Drug Reactions**

Classification	Drug(s)	Adverse Drug Reaction	Comments
A	β-blockers	Bradycardia	Dose dependent
A	ACEI	Cough	Switch ACEI to ARB
A	NSAIDs	GI bleeding	Interruption of mucosal barrier via COX-1 inhibition
A	Opiates	GI upset, constipation, urinary retention	Wean patients to lowest possible opioid dose
A	Acetaminophen	Hepatotoxicity	Depletes pools of glutathione allowing buildup of toxic metabolites
A	Vancomycin	Red Man Syndrome	Pruritic erythematous rash on upper body related to rapid infusion; histamine release Not considered an allergy
A	Aminoglycosides	Ototoxicity and nephrotoxicity	Dose dependent
B	Sulfa Drugs	Stevens-Johnson Syndrome Toxic Epidermal Necrolysis	Life threatening; do not rechallenge under any circumstance
B	Penicillins	Rash	Many children with EBV infection will develop a rash when given amoxicillin; this is NOT a true penicillin allergy
B	Valproic acid, Chinese herbs	Hepatotoxicity	Many other drugs are hepatotoxic (e.g. statins, OCPs, isoniazid)

**Sulfa-Containing Medications**

- Sulfamethoxazole
- Sulfasalazine
- Dapsone

## Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
  - the majority (but not all) of the patients will experience the desired therapeutic effect of a drug with minimal ADRs on the recommended dose
  - may need to adjust dosing or alter medication altogether
- possible causes of individual variability in drug response include problems with:
  - intake
    - ♦ patient adherence, e.g. hard to follow dosing schedule, unpalatable drug, costly drug
  - pharmacokinetics (review pages CP3-CP7)
    - ♦ absorption
      - decreased by vomiting, diarrhea or steatorrhea
      - first pass effect too high due to enzyme induction or too low due to liver disease
      - absorption change due to drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, fluoroquinolones)
    - ♦ distribution
      - very high or low percentage body fat, intact or disrupted BBB
      - patient is elderly or a neonate or has liver dysfunction
    - ♦ biotransformation and elimination
      - certain genetic polymorphisms or enzymes deficiencies to metabolize drugs (e.g. acetylcholinesterase deficiency, CYP polymorphism)
      - kidney or liver dysfunction or obstruction of bile elimination pathway
  - pharmacodynamics
    - ♦ genetic variability in drug response (e.g. malignant hyperthermia due to specific anesthetic agents)
    - ♦ disease process that affects drug pharmacodynamics
    - ♦ drug tolerance or cross-tolerance

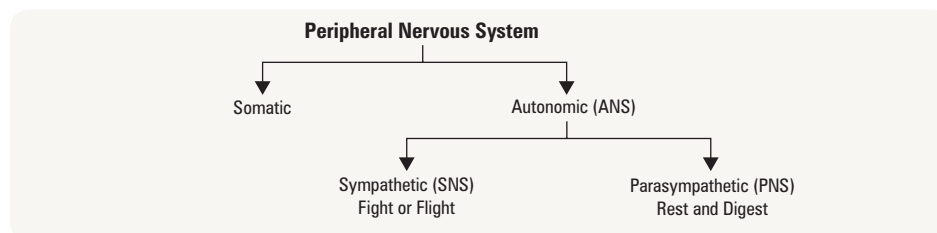
## Drug Interactions

- concomitant prescriptions: one drug alters the effect of another by changing its PK fate and/or PD action
- pharmacokinetic interactions involve:
  - absorption: alterations in gastrointestinal pH, gastric emptying, intestinal motility, gut mucosal function
  - biotransformation: alterations in drug metabolizing enzymes
  - excretion: alterations in renal elimination
- pharmacodynamic interactions are drug-induced alterations in the effects of other drugs due to exertion of similar changes to the body's physiology (additive) or opposing changes (subtractive)
- drug interactions can also involve herbal medications (e.g. St. John's Wort) and food (e.g. grapefruit)

**Table 5. Examples of Clinically Relevant Drug Interactions**

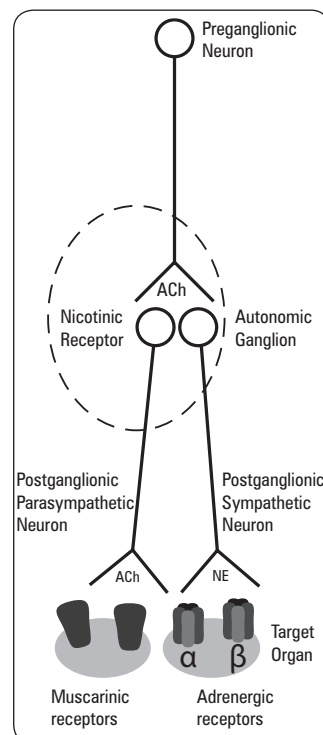
Interaction	Potential Effect	Comments
<b>Warfarin</b> plus ciprofloxacin, clarithromycin, erythromycin, metronidazole or trimethoprim-sulfamethoxazole	Increased effect of warfarin	Use alternative antibiotic Antibiotics inhibit intestinal production of vitamin K Inhibition of hepatic metabolism of warfarin
<b>Oral contraceptive pills</b> plus rifampin, antibiotics	Decreased effectiveness of oral contraception	Avoid if possible Increased metabolism of exogenous estrogen
<b>Sildenafil</b> plus nitrates	Hypotension	Absolute contraindication Vasodilatation
<b>SSRI</b> plus St. John's wort, naratriptan, rizatriptan, sumatriptan, zolmitriptan	Serotonin syndrome	Avoid if possible Monitor for signs and symptoms of serotonin syndrome
<b>SSRI</b> plus selegiline or non-selective MAO-I	Serotonin syndrome	Avoid Additive serotonergic effects
Some <b>HMG-CoA reductase inhibitors</b> plus niacin, gemfibrozil, erythromycin or itraconazole	Possible rhabdomyolysis	Avoid if possible

## Autonomic Pharmacology



**Figure 11. Subdivisions of the peripheral nervous system**

- most organs are innervated by both sympathetic and parasympathetic nerves; these have opposing effects (see [Neurology](#), Figure 8, N6)
- almost all **ANS efferent tracts** are divided into preganglionic and postganglionic nerves, which synapse in the autonomic ganglion (see Figure 12)
- **sympathetic preganglionic fibers** originate in the spinal cord at spinal levels T1-L3, and terminate in one of two ganglia
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. pre-vertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- **parasympathetic preganglionic fibers** originate in the lower brainstem from cranial nerves III, VII, IX, X, and in the sacral spinal cord at levels S2-S4; they terminate in the ganglionic cells located near or within the target organ
- blood vessels, sweat glands, spleen capsule, adrenals, do NOT have parasympathetic innervation



**Figure 12. Autonomic nervous system (ANS) efferent tracts**

## Parasympathetic Nervous System (PNS)

- **acetylcholine (ACh)** is the main neurotransmitter of the parasympathetic nervous system
- ACh receptors include
  - **nicotinic (pre-ganglionic) receptors** located in the autonomic ganglia
  - **nicotinic (post-ganglionic) receptors** in the adrenal medulla
  - **muscarinic (only post-ganglionic) receptors**
    - ♦  $M_1$  located in the CNS
    - ♦  $M_2$  receptors located on smooth muscle, cardiac muscle, and glandular epithelium
- ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase
  - e.g. acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) are used to increase ACh levels in conditions such as myasthenia gravis and Alzheimer's disease

## Sympathetic Nervous System (SNS)

- **norepinephrine (NE)** is the major neurotransmitter of the SNS
- **receptors** include
  - $\beta_1$ : predominately in cardiac tissue
  - $\beta_2$ : predominately in smooth muscle and glands
  - $\alpha_1$ : predominately on post-synaptic receptors in smooth muscles and glands
  - $\alpha_2$ : predominately on pre-synaptic terminals, where they feed back to inhibit further NE release; also exist as post-synaptic terminals in the brain, uterus, and vascular smooth muscle
- NE action is terminated by reuptake by the presynaptic membrane, diffusion from the synaptic cleft and degradation by **monoamine oxidase (MAO)** and **catechol-O-methyl transferase (COMT)**

**Table 6. Direct Effects of Autonomic Innervation on the Cardiorespiratory System**

Organ	Sympathetic Nervous System		Parasympathetic Nervous System	
	Receptor	Action	Receptor	Action
<b>Heart</b>				
1. Sinoatrial	$\beta_1$	Increased HR	M	Decreased conduction
2. Atrioventricular node	$\beta_1$	Increased conduction	M	Decreased conduction
3. Atria	$\beta_1$	Increased contractility	M	Decreased conduction
4. Ventricles	$\beta_1$	Increased contractility	M	Decreased HR
<b>Blood Vessels</b>				
1. Skin, splanchnic	$\alpha_1, \alpha_2$	Constriction	M	Dilatation
2. Skeletal muscle	$\alpha$	Constriction	M	Dilatation
	$\beta_2$ – large muscles	Dilatation	M	Dilatation
3. Coronary	$\alpha_1, \alpha_2$	Constriction	M	Dilatation
	$\beta_2$	Dilatation	M	Dilatation
<b>Lungs</b>				
1. Bronchiolar smooth muscle	$\beta_2$	Relaxation	M	Constriction
2. Bronchiolar glands	$\alpha_1, \beta_2$	Increased secretion	M	Stimulation

## Common Drug Endings

**Table 7. Common Drug Endings**

Ending	Category	Example
-afil	5-PDE inhibitor	sildenafil
-ane	Inhaled general anesthetic	halothane
-azepam	Benzodiazepine	lorazepam
-azole	Antifungal	ketoconazole
-caine	Local anesthetic	lidocaine
-olol	$\beta$ -blocker	propranolol
-prazole	Proton pump inhibitor	omeprazole
-pril	ACE inhibitor	captopril
-sartan	ARB	candesartan
-statin	HMG-CoA inhibitor	atorvastatin
-terol	$\beta_2$ agonist	albuterol
-tidine	H <sub>2</sub> antagonist	cimetidine
-tropin	Pituitary hormone	somatotropin
-vir	Antiviral	acyclovir
-zosin	$\alpha_1$ antagonist	prazosin

Note: Some medications are exceptions to the rule, e.g. methimazole (antithyroid)

## References

### Principles of Clinical Pharmacology

Hardman JG and Limbird LR. Goodman and Gilman's the pharmacological basis of therapeutics, 9th ed. New York: McGraw-Hill, 1996.

Hardy B and Bedard M. Compendium of pharmaceuticals and specialties. Ottawa: Canadian Pharmacists Association, 2002. Chapter: Serum drug concentration monitoring.

Kalant H, Grant DM, Mitchell J. Principles of medical pharmacology, 7th ed. Toronto: Elsevier Canada, 2007.

Katzung BG. Basic and clinical pharmacology, 8th ed. New York: McGraw-Hill, 2001.

Rang H, Dale M, Ritter J. Pharmacology, 4th ed. Edinburgh: Churchill Livingstone, 1999.

### Adverse Drug Reactions

Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J, et al. The Canadian adverse events study: the incidence of adverse events among hospital patients in Canada. CMAJ 2004;170:1678-1686.

Lewis T. Using the NO TEARS tool for medication review. BMJ 2004; 329:434.

MedEffect Canada. Canada vigilance adverse reaction online database (Internet). Ottawa: Health Canada. c1964 (updated 2011 Mar 31; cited 2011 Aug 20). Available from: [http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index_e.html).

Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park K and Breckenridge A. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18820 patients. BMJ 2004;329:315.

Samoy LJ, Zed PJ, Wilbur K, Balen RM, Abu-Laban RB and Roberts M. Drug-related hospitalizations in a tertiary care internal medicine service of a Canadian hospital: a prospective study. Pharmacotherapy 2006;26:1578-1586.

### Drug Interactions

Ament PW, Bertolino JG and Liszewski JL. Clinically significant drug interactions. Am Fam Physician 2000;61:1745-1754.

Indiana University, Division of Clinical Pharmacology. P450 drug interaction table (Internet). Indiana University; c2009 (updated 2011 Aug 18; cited 2011 Aug 20). Available from: <http://medicine.iupui.edu/clinpharm/DDIs/table.aspx>.



Amanda Carleton, Thanh-Cat Ho, Anjali Papneja and Yuliya Velykoredko, chapter editors

Maria Jogova and Howard Meng, associate editors

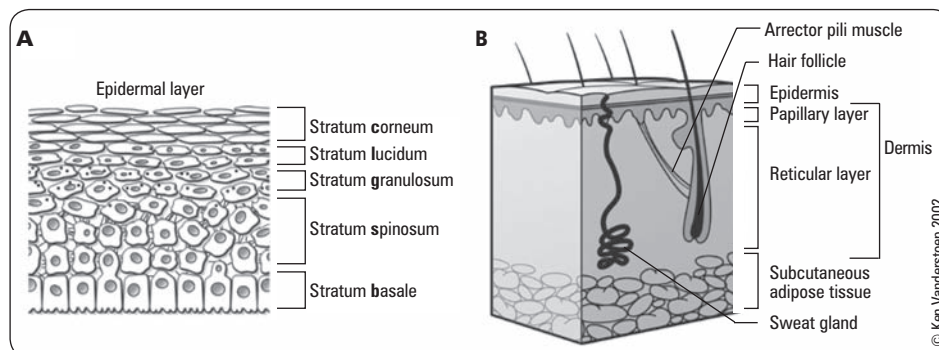
Melini Gupta, EBM editor

Dr. David Adam, Dr. Yvette Miller-Monthrope and Dr. Jensen Yeung, staff editors

<b>Acronyms</b> .....	<b>2</b>	<b>Heritable Disorders</b> .....	<b>23</b>
<b>Introduction to Skin</b> .....	<b>2</b>	Ichthyosis Vulgaris	
Skin Anatomy		Neurofibromatosis	
Skin Function		Vitiligo	
<b>Definitions</b> .....	<b>3</b>	<b>Infections</b> .....	<b>25</b>
Primary Morphological Lesions		Bacterial Infections	
Secondary Morphological Lesions		Dermatophytoses	
Other Morphological Lesions		Parasitic Infections	
Patterns and Distribution		Viral Infections	
<b>Differential Diagnoses of Common Presentations</b> .....	<b>5</b>	Yeast Infections	
<b>Common Skin Lesions</b> .....	<b>5</b>	Sexually Transmitted Infections	
Cysts		<b>Pre-Malignant Skin Conditions</b> .....	<b>32</b>
Fibrous Lesions		Actinic Keratosis (Solar Keratosis)	
Hyperkeratotic Lesions		Leukoplakia	
Keloids		<b>Malignant Skin Tumours</b> .....	<b>33</b>
Pigmented Lesions		Non-Melanoma Skin Cancers	
Vascular Lesions		Basal Cell Carcinoma (BCC)	
<b>Acneiform Eruptions</b> .....	<b>11</b>	Squamous Cell Carcinoma (SCC)	
Acne Vulgaris/Common Acne		Other Forms of Squamous Cell Carcinoma (SCC)	
Perioral Dermatitis		Malignant Melanoma (MM)	
Rosacea		Other Cutaneous Cancers	
<b>Dermatitis (Eczema)</b> .....	<b>13</b>	Cutaneous T-cell Lymphoma	
Asteatotic Dermatitis		<b>Alopecia (Hair Loss)</b> .....	<b>37</b>
Atopic Dermatitis		Hair Growth	
Contact Dermatitis		Non-Scarring (Non-Cicatricial) Alopecia	
Dyshidrotic Dermatitis		Scarring (Cicatricial) Alopecia	
Nummular Dermatitis		<b>Nails and Disorders of the Nail Apparatus</b> ..	<b>39</b>
Seborrheic Dermatitis		<b>Skin Manifestations of Systemic Disease</b> ...	<b>39</b>
Stasis Dermatitis		<b>Pediatric Exanthems</b> .....	<b>40</b>
Lichen Simplex Chronicus		<b>Miscellaneous Lesions</b> .....	<b>41</b>
<b>Papulosquamous Diseases</b> .....	<b>17</b>	Angioedema and Urticaria	
Lichen Planus		Erythema Nodosum	
Pityriasis Rosea		Pruritus	
Psoriasis		Wounds and Ulcers	
<b>Vesiculobullous Diseases</b> .....	<b>20</b>	<b>Common Medications</b> .....	<b>43</b>
Bullous Pemphigoid		Sunscreens and Preventative Therapy	
Pemphigus Vulgaris		Topical Steroids	
Dermatitis Herpetiformis		Dermatologic Therapies	
Porphyria Cutanea Tarda		<b>References</b> .....	<b>47</b>
<b>Drug Eruptions</b> .....	<b>22</b>		
Drug Hypersensitivity Syndrome			
Erythema Multiforme (EM)			
Stevens-Johnson Syndrome (SJS)			
Toxic Epidermal Necrolysis (TEN)			
Exanthematous Eruptions (Maculopapular Eruptions/Morbiliform)			
Fixed Drug Eruptions			
Photosensitivity Eruptions			
Serum Sickness-Like Reaction			

# Introduction to Skin

## Skin Anatomy



**Figure 1. Histologic layers of the skin.** Epidermal layer is detailed in A

### Skin

- divided anatomically into epidermis, dermis, and subcutaneous tissue
- epidermis**
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale (Figure 1A)
  - cells progress from stratum basale to stratum corneum in about 4 wk
    - stratum basale (germinativum): mitotic figures that give rise to keratinocytes
    - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
    - stratum granulosum: flat cells containing basophilic granules which characterize skin
    - stratum lucidum: comprised of transparent layers of packed dead cells
    - stratum corneum: flat scales of the water-resistant protein keratin
- dermis**: comprised of connective tissue divided into two regions (Figure 1B):
  - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
  - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages
- subcutaneous tissue** (subdermal)
  - consists primarily of adipose cells, larger caliber vessels, nerves and fascia

### Cells in Epidermis

- keratinocytes**: located in all layers of the epidermis, except the stratum corneum; connected to each other by desmosomes
- melanocytes**: located in the stratum basale; keratinocyte to melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races
- Langerhans cells**: important for immune surveillance
- Merkel cells**: involved in touch sensation

### Skin Appendages

- epidermal in origin; can extend into the dermis, includes hair, nails, and cutaneous glands

### Cutaneous Glands

- sebaceous gland**: part of pilosebaceous unit, produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
  - sebum has some antifungal properties
  - these glands cover entire skin surface except palms and soles
- apocrine sweat gland**: apocrine duct empties into hair follicle above sebaceous gland
  - found in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)
- eccrine sweat gland**: not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface



### Layers of the Epidermis

"Californians Like Getting Sun Burns"

## Acronyms

β-hCG	beta-human chorionic gonadotropin
AAFP	American Association of Family Physicians
AD	atopic dermatitis
AK	actinic keratosis
ASA	acetylsalicylic acid
ASO	anti-streptolysin O
BCC	basal cell carcinoma
BSA	body surface area
BUN	blood urea nitrogen
C&S	culture and sensitivity
CBC	complete blood count
CMV	cytomegalovirus
CNS	central nervous system
Cr	creatinine
DLE	discoid lupus erythematosus
DM	diabetes mellitus
DVT	deep vein thrombosis
EM	erythema multiforme
ESR	erythrocyte sedimentation rate
Fe	iron
FTA-ABS	fluorescent treponemal antibody-absorption
GAS	group A β-hemolytic <i>Streptococcus</i>
GVHD	graft-versus-host disease
HHV	human herpes virus
HPA	hypothalamic-pituitary-adrenal
HPV	human papilloma virus
HRT	hormone replacement therapy
HSV	herpes simplex virus
HZV	herpes zoster virus
IFN	interferon
IVIG	intravenous immunoglobulin
LFT	liver function test
MAOI	monoamine oxidase inhibitor
MM	malignant melanoma
MMR	measles/mumps/rubella
MTP	metatarsal phalangeal
NB-UVB	narrow band ultraviolet wavelength B
NCN	neocellular nevus
Nd: Yag	neodymium-doped yttrium aluminum garnet
NMN	nevomelanocytic nevi
NMSC	non-melanoma skin cancers
NSAID	nonsteroidal anti-inflammatory drug
OC	oral contraceptive pill
OTC	over-the-counter
PABA	para-aminobenzoic acid
PASI	Psoriasis Area and Severity Index
PPD	purified protein derivative
PUVA	psoralens and long wave ultraviolet radiation
RA	rheumatoid arthritis
SCC	squamous cell carcinoma
SHBG	sex hormone-binding globulin
SJS	Stevens-Johnson Syndrome
SLE	systemic lupus erythematosus
SPF	sun protection factor
SSRI	selective serotonin reuptake inhibitor
SSSS	staphylococcal scalded skin syndrome
STI	sexually transmitted infection
TB	tuberculosis
TEN	toxic epidermal necrolysis
TMP/SMX	trimethoprim-sulfamethoxazole
TSH	thyroid stimulating hormone
UC	ulcerative colitis
URTI	upper respiratory tract infection
UV	ultraviolet
UVA	ultraviolet wavelength A
UVB	ultraviolet wavelength B
UVC	ultraviolet wavelength C
VDRL	venereal disease research laboratory
VZV	varicella zoster virus

© Ken Vanderstoep 2002

## Skin Function

- **protection**
  - due to continuous recycling and avascularity of epidermis
  - barrier to: UV radiation, mechanical/chemical insults, pathogens and dehydration
- **thermal regulation**
  - insulation to maintain body temperature in cool environments, via peripheral vasoconstriction, hair and subcutaneous adipose tissue
  - dissipation of heat in warm environments, via increased activity of sweat glands and increased blood flow within dermal vascular networks
- **sensation**
  - touch, pain, and temperature sensation
- **metabolic function**
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

## Definitions

### Primary Morphological Lesions

#### Definition

- an initial lesion that has not been altered by trauma or manipulation and has not regressed
- **macule**: flat lesion <1 cm
- **patch**: flat lesion ≥1 cm
- **papule**: elevated, palpable lesion <1 cm
- **plaque**: elevated, palpable lesion ≥1 cm
- **nodule**: deep, palpable lesion <1 cm, often dermal or subcutaneous in origin
- **tumour**: deep, palpable lesion ≥1 cm
- **vesicle**: fluid-filled lesion <1 cm
- **bulla**: fluid-filled lesion ≥1 cm
- **cyst**: an epithelial-lined collection containing semi-solid or fluid material
- **pustule**: an elevated lesion containing purulent fluid (white, grey, yellow, green)
- **erosion**: a disruption of the skin involving the epidermis alone; heals without scarring
- **ulcer**: a disruption of the skin that extends into the dermis or deeper; heals with scarring
- **indurated**: descriptive term for a lesion that is hard or firm
- **scar**: replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- **wheel**: a special form of papule or plaque that is blanchable and transient, formed by edema in the dermis (e.g. urticaria)

Table 1. Types of Lesions

Profile	<1 cm Diameter	≥1 cm Diameter
Flat lesion	Macule (e.g. freckle)	Patch (e.g. vitiligo)
Raised superficial lesion	Papule (e.g. wart)	Plaque (e.g. psoriasis)
Deep palpable (dermal or subcutaneous)	Nodule (e.g. dermatofibroma)	Tumour (e.g. lipoma)
Elevated fluid-filled lesions	Vesicle (e.g. HSV)	Bulla (e.g. bullous pemphigoid)



#### Describe a Lesion with SCALDA

**Size and Surface area**  
**Colour** (e.g. hyperpigmented, hypopigmented, erythematous)  
**Arrangement** (e.g. solitary, linear, reticulated, grouped, herpetiform)  
**Lesion morphology** (see Table 1)  
**Distribution** (e.g. dermatomal, intertriginous, symmetrical/asymmetrical, follicular)  
**Always check hair, nails, mucous membranes and intertriginous areas**



#### Skin Phototypes (Fitzpatrick)

Phototype	Colour of Skin	Skin's Response to Sun Exposure (without SPF protection)
I	White	Always burns, never tans
II	White	Always burns, little tan
III	White	Slight burn, slow tan
IV	Pale brown	Slight burn, faster tan
V	Brown	Rarely burns, dark tan
VI	Dark brown or black	Never burns, dark tan

## Secondary Morphological Lesions

#### Definition

- develop during the evolutionary process of skin disease, or created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)
- **crust**: dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- **scale**: excess keratin (e.g. seborrheic dermatitis)
- **lichenification**: thickening of the skin and accentuation of normal skin markings (e.g. chronic atopic dermatitis)
- **fissure**: a linear slit-like cleavage of the skin
- **excoriation**: a scratch mark
- **xerosis**: pathologic dryness of skin (xeroderma), conjunctiva (xerophthalmia), or mucous membranes
- **atrophy**: histological decrease in size and number of cells or tissues, resulting in thinning or depression of the skin

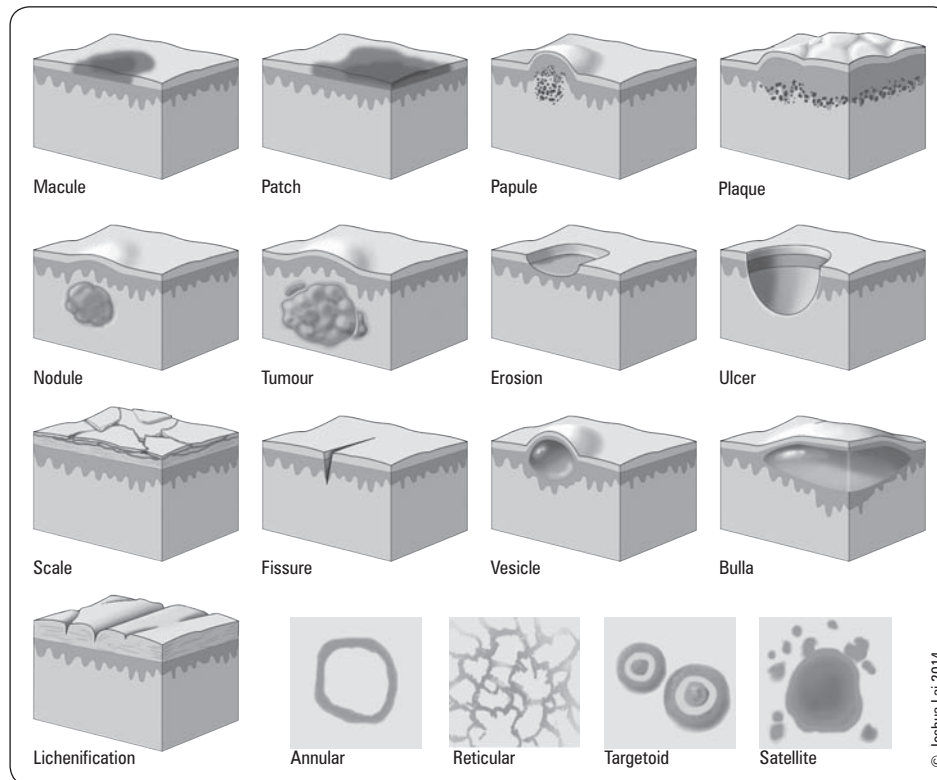


Figure 2. Examples of primary and secondary morphology

## Other Morphological Lesions

- **comedones**: collection of sebum and keratin
  - open comedo (blackhead)
  - closed comedo (whitehead; differentiated from pustule)
- **purpura**: extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, 3 mm-1 cm in size
  - **petechiae**: small pinpoint purpura, <3 mm in size
  - **ecchymoses**: larger flat purpura, >1 cm in size, aka a “bruise”
- **telangiectasia**: dilated superficial blood vessels; blanchable

## Patterns and Distribution

- **acral**: relating to the hands and feet (e.g. hand, foot and mouth disease)
- **annular**: ring-shaped (e.g. granuloma annulare)
- **follicular**: involving hair follicles (e.g. folliculitis)
- **guttate**: lesions following a “drop-like” pattern (e.g. guttate psoriasis)
- **Koebner phenomenon**: aka isomorphic response, appearance of lesions at an injury site (e.g. lichen planus, psoriasis, vitiligo). An isomorphic reaction that develops in areas of trauma (linear exposure, excoriation), after the traumatic event. This can be differentiated from other lesions by arrangement, as Koebner phenomena may not follow dermatomes or the lines of Blaschko
- **morbilliform**: a maculopapular rash resembling measles
- **reticular**: lesions following a net-like pattern (e.g. livedo reticularis)
- **satellite**: lesions scattered outside of primary lesion (e.g. candida diaper dermatitis)
- **serpiginous**: lesions following a snake-like pattern (e.g. cutaneous larva migrans)
- **target/targetoid**: concentric ring lesions, like a dartboard (e.g. EM)
- **other descriptive terms**: discrete, clustered, linear, confluent, dermatitic, indurated

## Differential Diagnoses of Common Presentations

Table 2. Differential Diagnosis of Common Presenting Problems

Lesion	Infectious	Inflammatory	Drug/Toxin	Miscellaneous
<b>Brown Macule</b>		Post-inflammatory hyper-pigmentation	UV radiation, actinic/solar lentigo, freckle (ephelide)	Congenital: café-au-lait spots, congenital nevus, epidermal/junctional nevus Neoplasia: lentigo maligna, malignant melanoma, pigmented BCC Other: melasma/chloasma ("mask of pregnancy")
<b>Discrete Red Papule</b>	Folliculitis Furuncle Scabies	Acne vulgaris Lichen planus Rosacea Psoriasis Urticaria	Bites/stings	Vascular: hemangioma, pyogenic granuloma Other: dermatofibroma, miliaria rubra
<b>Red Scales</b>	Pityriasis rosea Secondary syphilis Tinea	Dermatitis (atopic, contact, nummular, seborrheic) Discoid lupus Lichen planus Psoriasis	Gold	Neoplastic: mycosis fungoides
<b>Vesicle</b>	Cat-Scratch disease Impetigo Viral: HSV, HZV, VZV, Molluscum, Coxsackie Scabies	Acute contact dermatitis Dyshidrotic eczema		Other: dermatitis herpetiformis, porphyria cutanea tarda
<b>Bulla</b>	Bullous impetigo	Acute dermatitis EM, SJS, TEN, SLE	Fixed drug eruption	Autoimmune: bullous pemphigoid, pemphigus vulgaris Other: dermatitis herpetiformis, porphyria cutanea tarda
<b>Pustule</b>	Candida Dermatophyte Impetigo Sepsis Varicella	Acne vulgaris Rosacea Dyshidrotic dermatitis Pustular folliculitis Pustular psoriasis	Acute generalized exanthematous pustulosis (usually secondary to drug reaction)	Other: hidradenitis suppurativa
<b>Oral Ulcer</b>	Aspergillosis CMV Coxsackie Cryptococcosis HSV/HZV HIV, TB, Syphilis	Allergic stomatitis EM/SJS/TEN Lichen planus Seronegative arthropathies, SLE Recurrent aphthous stomatitis Behçet's disease	Chemotherapy Radiation therapy	Autoimmune: pemphigus vulgaris Congenital: XXY Hematologic: sickle cell disease Neoplasia: BCC, SCC
<b>Skin Ulcer</b>	Plague Syphilis TB Tularemia	RA, SLE, vasculitis UC (pyoderma gangrenosum)		Autoimmune: necrobiosis lipoidica diabetorum (e.g. DM) Congenital: XXY Hematologic: sickle cell disease Neoplasia: SCC Vascular: arterial, neurotropic, pressure, venous, aphthous, leukoplakia, traumatic

## Common Skin Lesions

### Cysts



Table 3. Cysts

	Epidermal Cyst	Pilar Cyst (Trichilemmal)	Dermoid Cyst	Ganglion Cyst	Milium
<b>Clinical Presentation</b>	Round, yellow/flesh coloured, slow growing, mobile, firm, fluctuant, nodule or tumour	Multiple, hard, variable sized nodules under the scalp, lacks central punctum	Most commonly found at lateral third of eyebrow or midline under nose	Usually solitary, rubbery, translucent; a clear gelatinous viscous fluid may be extruded	1-2 mm superficial, white to yellow subepidermal papules occurring on eyelids, cheeks, and forehead
<b>Pathophysiology</b>	Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris May be post-traumatic, rarely syndromic	Thick-walled cyst lined with stratified squamous epithelium and filled with dense keratin Idiopathic Post-trauma, often familial	Rare, congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick walled cyst filled with dense keratin	Cystic lesion that originates from joint or tendon sheath, called a digital mucous cyst when found on fingertip Associated with osteoarthritis	Small epidermoid cyst, primarily arising from pluripotential cells in epidermal or adnexal epithelium can be secondary to blistering, ulceration, trauma, topical corticosteroid atrophy, or cosmetic procedures
<b>Epidemiology</b>	Most common cutaneous cyst in youth – mid age	2nd most common cutaneous cyst F>M	Rare	Older age	Any age 40-50% of infants
<b>Clinical Course</b>	Central punctum may rupture (foul, cheesy odour, creamy colour) and produce inflammatory reaction Increase in size and number over time, especially in pregnancy	Rupture causes pain and inflammation	If nasal midline, risk of extension into CNS	Stable	In newborns, spontaneously resolves in first 4 wk of life
<b>Management</b>	Excise completely before it becomes infected	Excision	Excision	Drainage ± steroid injection if painful Compression daily for 6 wk Excision if bothersome	Incision and expression of contents Laser ablation and electrodesiccation Multiple facial milia respond to topical retinoid therapy

## Fibrous Lesions



### DERMATOFIBROMA

#### Clinical Presentation

- button-like, firm dermal papule or nodule, skin-coloured to red-brown colouring
- majority are asymptomatic but may be pruritic and/or tender
- site: legs > arms > trunk
- dimple sign: lateral compression causes dimpling of the lesion

#### Pathophysiology

- benign tumour due to fibroblast proliferation in the dermis

#### Etiology

- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibromata can be associated with SLE

#### Epidemiology

- adults, F>M

#### Differential Diagnosis

- dermatofibrosarcoma protuberans, malignant melanoma, Kaposi's sarcoma, blue nevus

#### Investigations

- biopsy if diagnosis is uncertain

#### Management

- no treatment required
- excision or cryosurgery if bothersome

### SKIN TAGS

#### Clinical Presentation

- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

#### Pathophysiology

- benign outgrowth of skin

#### Epidemiology

- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

#### Differential Diagnosis

- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma, fibroepithelioma of Pinkus (rare variant of BCC)

#### Management

- excision, electrodesiccation, cryosurgery



#### Skin tags are also known as...

- Acrochordons
- Fibroepithelial polyps
- Soft fibromas
- Pedunculated lipofibromas
- Cutaneous papillomas

## Hyperkeratotic Lesions



### SEBORRHEIC KERATOSIS



#### Clinical Presentation

- well-demarcated waxy papule/plaque with classic "stuck on" appearance
- large variety in colour, size and shape
- over time lesions appear more warty, greasy and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

#### Pathophysiology

- very common benign epithelial tumour

#### Epidemiology

- unusual <30 yr old
- autosomal dominant inheritance

#### Differential Diagnosis

- malignant melanoma (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented actinic keratosis



**Investigations**

- biopsy only if diagnosis uncertain

**Management**

- none required, for cosmetics only
- cryotherapy, curettage

**ACTINIC KERATOSIS (SOLAR KERATOSIS)****Clinical Presentation**

- ill-defined, scaly erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

**Pathophysiology**

- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of actinic keratosis (AK) to SCC (~1/1000), but higher likelihood if AK is persistent

**Epidemiology**

- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III (see sidebar, D3), rare in darker skin as melanin is protective

**Differential Diagnosis**

- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

**Investigations**

- biopsy lesions that are refractory to treatment

**Management**

- destructive: cryotherapy, electrodesiccation and curettage
- pharmacotherapy: 5-fluorouracil cream for 2-3 wk, imiquimod cream for 8-10 wk, photodynamic therapy

**KERATOACANTHOMA****Clinical Presentation**

- rapidly growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled crater, resembling an erupting volcano
- often spontaneously regresses within a year, leaving a scar
- sites: sun-exposed skin

**Pathophysiology**

- epithelial neoplasm with atypical keratinocytes in epidermis
- low grade variant of SCC

**Etiology**

- HPV, UV radiation, chemical carcinogens (tar, mineral oil)

**Epidemiology**

- >50 yr, rare <20 yr

**Differential Diagnosis**

- treat as SCC until proven otherwise
- hypertrophic solar keratosis, verruca vulgaris

**Management**

- surgical excision, treated similarly to SCC

**CORNS****Clinical Presentation**

- firm papule with a central, translucent, cone-shaped, hard keratin core
- painful with direct pressure
- sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

**Pathophysiology**

- localized hyperkeratosis induced by pressure on hands and feet

**Corns vs. Warts vs. Calluses**

- **Corns** have a whitish yellow central translucent keratinous core. Painful with direct pressure
- **Warts** bleed with paring and have a black speckled central appearance due to thrombosed capillaries. Plantar warts destroy dermatoglyphics (epidermal ridges)
- **Calluses** have layers of yellowish keratin revealed with paring. There are no thrombosed capillaries or interruption of epidermal ridges

### Epidemiology

- F>M, can be caused by chronic microtrauma

### Differential Diagnosis

- tinea pedis, plantar warts

### Management

- relieve pressure with padding or alternate footwear, orthotics
- paring, curettage

## Keloids

### Clinical Presentation

- firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
- extends beyond the margins of the original injury, and may continue to expand in size for years with claw-like extensions
- can be pruritic and painful
- sites: earlobes, shoulders, sternum, scapular area

### Pathophysiology

- excessive deposition of randomly organized collagen fibers following trauma to skin
- differentiated from a hypertrophic scar which is confined to the borders of the original injury

### Epidemiology

- most common in black patients, followed by those of Asian descent (predilection for darker skin)
- M=F, all age groups

### Management

- intralesional corticosteroid injections
- cryotherapy
- silicone compression



#### Keloids vs. Hypertrophic Scars

- **Keloids:** extend beyond margins of original injury with claw-like extensions
- **Hypertrophic scars:** confined to original margins of injury

## Pigmented Lesions

Table 4. Comparison of Pigmented Lesions

	Ephelides (Freckles)	Solar Lentigo (Liver Spot)	Dermal Melanocytosis (historically known as Mongolian Spot)	Becker's Nevus
<b>Clinical Presentation</b>	Small (<5 mm) well-demarcated light brown macules Sites: sun-exposed skin	Well-demarcated brown/black irregular macules Sites: sun-exposed skin	Congenital grey-blue solitary or grouped macules commonly on lumbosacral area	Hairy, light brown macule/patch with a papular verrucous surface Sites: trunk and shoulders, onset in teen years
<b>Pathophysiology</b>	Increased melanin within basal layer keratinocytes secondary to sun exposure	Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure	Ectopic melanocytes in dermis	Pigmented hamartoma with increased melanin in basal cells
<b>Epidemiology</b>	Skin phototypes I and II	Most common in Caucasians >40 yr Skin phototype I-III	99% occurs in Asian and Aboriginal infants	M>F Often becomes noticeable at puberty
<b>Differential Diagnosis</b>	Junctional nevi Juvenile lentiginos	Lentigo maligna, seborrheic keratosis, pigmented solar keratosis	Ecchymosis	Hairy congenital melanocytic nevus
<b>Clinical Course and Management</b>	No treatment required Multiply and darken with sun exposure, fade in winter Sunscreen may prevent the appearance of new freckles	Laser therapy, shave excisions, cryotherapy	Usually fades in early childhood but may persist into adulthood	Hair growth follows onset of pigmentation Cosmetic management (usually too large to remove)



#### DDx of Hyperpigmented Macules

- Purpura (e.g. solar, ASA, anti-coagulants, steroids, hemosiderin stain)
- Post-inflammatory
- Melasma
- Melanoma
- Fixed drug eruption

**NEVOMELANOCYTIC NEVI (NMN)** (see Table 5)

- common mole
- be suspicious of new or changing pigmented lesions (signs of melanoma)
- average number of moles per person: 18-40
- 3 stages of evolution:
  - junctional NMN: macular; arise at dermal-epidermal junction
  - compound NMN: papular; nevus cells invade the papillary dermis
  - dermal NMN: skin coloured papules (no longer hyperpigmented); nevus cells completely migrate into dermis

**Table 5. Nevomelanocytic Nevus Classification**

Type	Age of Onset	Clinical Presentation	Histology	Management
<b>Congenital</b>	Birth and early infancy	Sharply demarcated pigmented brown plaque with regular/irregular contours ± coarse hairs Consider meningeal involvement if very large or bathing suit distribution	Nevomelanocytes in epidermis (clusters) and dermis (strands)	Surgical excision if suspicious, due to increased risk of melanoma
<b>Acquired</b>	Early childhood to age 40 Involute by age 60	Benign neoplasm of pigment-forming nevus cell Well circumscribed, round, uniformly pigmented macules/papules <1.5 cm Classified according to site of nevus cells		Excisional biopsy can be considered if on scalp, soles, mucous membranes, anogenital area, or if varied colours, irregular borders, pruritic, bleeding, exposed to trauma
<b>Junctional</b>	Childhood Majority progress to compound nevus	Flat, irregularly bordered, uniformly tan-dark brown, sharply demarcated smooth macule	Melanocytes at dermal-epidermal junction above basement membrane	Same as above
<b>Compound</b>	Any age	Domed, regularly bordered, smooth, round, tan-dark brown papule Face, trunk, extremities, scalp NOT found on palms or soles	Melanocytes at dermal-epidermal junction; migration into dermis	Same as above
<b>Dermal</b>	Adults	Soft, dome-shaped, skin-coloured to tan/brown papules or nodules, often with telangiectasia Sites: face, neck	Melanocytes exclusively in dermis	Same as above
<b>Dysplastic</b>	Childhood	Variegated macule/papule with irregular indistinct melanocytes in the basal cell layer Risk factors: positive family history	Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus Often with region of adjacent nests	Follow with colour photographs for changes Excisional biopsy if lesion changing or highly atypical

**ABCDE of Melanoma**

**A**symmetry  
**B**orders (irregular)  
**C**olour (variegated)  
**D**iameter (>6 mm)  
**E**volution (over time)

**Other Nevi**

- **Halo nevus:** often a typical appearing nevus surround by a ring of depigmentation; not rare in children; uncommonly associated with vitiligo; no treatment required unless irregular colour or borders
- **Blue nevus:** round to oval macule/papule with homogenous blue to blue-black colour. Often appears in childhood and late adolescence; no treatment required unless atypical features are noted

**MELASMA****Clinical Presentation**

- dark skin discoloration on sun-exposed areas of face (forehead, upper lip, cheeks, chin)
- usually symmetrical

**Pathophysiology**

- increase in number and activity of melanocytes
- associated with estrogen and progesterone
- classification determined by depth of hyperpigmentation in the skin (epidermal, dermal, mixed type)
- epidermal pigmentation is most common and can be diagnosed with Wood's light

**Epidemiology**

- F>>M
- common in pregnancy (chloasma = "mask of pregnancy") and women taking OCP and HRT
- risk factors include sun exposure and dark skin tone
- can occur with mild endocrine disturbances, antiepileptic medications and other photosensitizing drugs

### Management

- bleaching cream (hydroquinone), retinoic acid, topical steroids or combination creams
- destructive modalities (chemical peels, laser treatment)
- camouflage make-up
- avoiding sun and using sunscreen are key to preventing melasma
- often fades over several months after stopping hormone treatment or delivering baby

## Vascular Lesions



**Table 6. Vascular Tumours Compared to Vascular Malformations**

	Vascular Tumours	Vascular Malformations
<b>Definition</b>	Endothelial hyperplasia	Congenital malformation with normal endothelial turnover
<b>Presence at Birth</b>	Usually postnatal	100% at birth (not always obvious)
<b>M:F</b>	1:3-5	1:1
<b>Natural History</b>	Phases: <ul style="list-style-type: none"> <li>• Proliferating</li> <li>• Involuting</li> <li>• Involved</li> </ul>	Proportionate growth (can expand)

### HEMANGIOMAS

#### Clinical Presentation

- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a “bag of worms” when palpated

#### Pathophysiology

- benign vascular tumour
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

**Table 7. Vascular Tumours**

	Capillary Hemangioma	Spider Angioma (Campbell telangiectasia)	Cherry Angioma (Campbell De Morgan spot)	Pyogenic Granuloma
<b>Clinical Presentation</b>	Hot, firm red to blue plaques or tumours	Central red arteriole with slender branches, faintly pulsatile, blanchable Sites: face, forearms, and hands	Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm Site: trunk Less friable compared to pyogenic granulomas	Bright red, dome-shaped sessile or pedunculated friable nodule Sites: fingers, lips, mouth, trunk, toes DDx: glomus tumour, nodular malignant melanoma, SCC, nodular BCC
<b>Pathophysiology</b>	Benign vascular proliferation of endothelial lining	Associated with hyperestrogenic state (e.g. in hepatocellular disease, pregnancy, OCP)	Benign vascular neoplasm	Rapidly developing hemangioma Proliferation of capillaries with erosion of epidermis and neutrophilia
<b>Epidemiology</b>	Appears shortly after birth; rarely may be congenital		>30 yr old	<30 yr old
<b>Clinical Course</b>	Appears shortly after birth, increases in size over months, then regresses 50% of lesions resolve spontaneously by 5 yr	Increase in number over time	Lesions do not fade in time Lesions bleed infrequently	
<b>Management</b>	10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis Consider treatment if not gone by school age; Propranolol; systemic corticosteroids; laser treatment; surgery	Electro or laser surgery Systemic corticosteroids and IFN- $\alpha$ may be indicated for rapidly growing lesions	Usually no treatment needed Laser or electrocautery for small lesions Excision of large lesions if necessary	Surgical excision with histologic examination Electrocautery; laser; cryotherapy



A spider angioma will blanch when the tip of a paperclip is applied to the centre of the lesion.



Pyogenic Granuloma is a misnomer: it is neither pyogenic nor granulomatous.

## VASCULAR MALFORMATIONS

### 1. Nevus Flammeus (Port-wine stain)

#### Clinical Presentation

- red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline
- most common site: nape of neck

#### Pathophysiology

- congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution)

#### Management

- laser or make-up

### 2. Nevus Simplex (salmon patch)

#### Clinical Presentation

- pink-red irregular patches
- midline macule on glabella known as “Angel Kiss”; on nuchal region known as “Stork Bites”
- present in 1/3 of newborns
- majority regress spontaneously

#### Pathophysiology

- congenital dilation of dermal capillaries

#### Management

- no treatment required

## Acneiform Eruptions

### Acne Vulgaris/Common Acne

#### Clinical Presentation

- a common inflammatory pilosebaceous disease categorized with respect to severity
  - Type I: comedonal, sparse, no scarring
  - Type II: comedonal, papular, moderate  $\pm$  little scarring
  - Type III: comedonal, papular, and pustular, with scarring
  - Type IV: nodulocystic acne, risk of severe scarring
- sites of predilection: face, neck, upper chest, and back

#### Pathogenesis

- hyperkeratinization, at the follicular ostia (opening), blocks the secretion of sebum (microcomedones)
- androgens stimulate sebaceous glands to produce sebum
- anaerobic diphtheroid *Propionibacterium acnes* bacteria contains lipase, which converts sebum to free fatty acids and produces pro-inflammatory mediators

#### Epidemiology

- age of onset in puberty (10-17 yr in females, 14-19 yr in males)
- in prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital adrenal hyperplasia)
- more severe in males than in females
- incidence decreases in adulthood
- genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

#### Differential Diagnosis

- folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

#### Management

- see Table 8



A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone.



#### Intralesional Injections

Intralesional corticosteroid injections are effective in the treatment of individual acne nodules.



#### Acne Myths Debunked

- Eating greasy food and chocolate does not cause or worsen acne
- Blackheads (comedones) are black because of oxidized fatty acids, not dirt
- Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator



#### Acne Exacerbating Factors

- Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danazol
- Topical agents: steroids, tars, ointments, oily cosmetics
- Mechanical pressure or occlusion, such as leaning face on hands
- Emotional stress

Table 8. Management of Acne

Drug Name	Mechanism of Action	Notes
<b>MILD ACNE: Topical Therapies Over-the-Counter</b>		
<b>Benzoyl peroxide</b>	Bactericidal agent (targets <i>P. acnes</i> ) and comedolytic	Helps prevent <i>P. acnes</i> resistance
<b>Salicylic acid</b>	Comedolytic	Used when patients cannot tolerate a topical retinoid due to skin irritation
<b>MILD ACNE: Prescription Topical Therapies</b>		
<b>Clindamycin phosphate (e.g. Dalacin T<sup>®</sup>)</b>	Lincosamide antibiotic; inhibits protein synthesis	High rate of resistance when used as monotherapy
<b>Erythromycin</b>	Macrolide antibiotic; inhibits protein synthesis	High rate of resistance when used as monotherapy
<b>BenzaClin<sup>®</sup> gel</b>	1% clindamycin and 5% benzoyl peroxide	See above
<b>Erythromycin + benzoyl peroxide (Benzamycin<sup>®</sup>)</b>	3% erythromycin and 5% benzoyl peroxide	See above
<b>Adapalene (e.g. Differin<sup>®</sup>)</b>	Comedolytic	Less irritating than tretinoin. Not photolabile
<b>Tretinoin (e.g. Retin-A<sup>®</sup>)</b>	Comedolytic	Photolabile and irritation
<b>Adapalene + benzoyl peroxide (e.g. Tactuo<sup>®</sup>)</b>	0.1% adapalene and 2.5% benzoyl peroxide	See above
<b>MODERATE ACNE:</b> After topical treatments have failed, add oral antibiotics, such as tetracycline (250 mg PO bid to 500 mg bid), or erythromycin (500 mg PO bid). Antibiotics require 3-6 mo of use before assessing efficacy. Consider hormonal therapy, including antiandrogens		
<b>Tetracycline</b>	Inhibits protein synthesis	Use caution with regard to drug interactions: do not use with isotretinoin. Sun sensitivity
<b>Cyproterone acetate-ethinyl estradiol (Diane-35<sup>®</sup>)</b>	Cyproterone: potent anti-androgenic, progestogenic and antigonadotrophic activity Ethinyl estradiol: increases level of SHBG, reducing circulating plasma levels of androgens	After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance
<b>Spironolactone (source ADA)</b>	Blocks androgen receptors Dosages of 50 mg to 200 mg have been shown to be effective in hormonal acne	May cause hyperkalemia at higher doses Black box warning for breast cancer
<b>SEVERE ACNE:</b> Consider systemic retinoids after above treatments have failed or if significant scarring present		
<b>Isotretinoin (Accutane<sup>®</sup>, Clarus<sup>®</sup>)</b>	Retinoid that inhibits sebaceous gland function and regulates keratinization	See Table 29, D46 for full side effect profile Most adverse effects are temporary and will resolve when the drug is discontinued Baseline lipid profile (risk of hypertriglyceridemia), LFTs and $\beta$ -hCG before treatment May transiently exacerbate acne before patient sees improvement Drug may be discontinued at 16-20 wk when nodule count has dropped by >70% A second course may be initiated after 2 mo pm Refractory cases may require multiple courses of isotretinoin

**Accutane and Pregnancy**

- Use of Accutane<sup>®</sup> during pregnancy is associated with spontaneous abortion and major birth defects such as facial dysmorphism and cognitive impairment
- Pregnancy should be ruled out before starting Accutane<sup>®</sup>
- Ideally, patients should use 2 forms of contraception while on Accutane<sup>®</sup>

**Treatment of Acne Scars**

- Tretinoin creams
- Microdermabrasion for superficial scars
- Injectable fillers (collagen, hyaluronic acid)
- Fraxel laser

**Important Controversies Associated with Isotretinoin Therapy for Acne**

*Am J Clin Dermatol* 2013;14:71-76

**Study:** Review on isotretinoin and (1) depression and suicide, (2) inflammatory bowel disease (IBD), (3) pregnancy prevention programs.

**Conclusions:**

1. The evidence on whether isotretinoin causes depression and suicide is inconsistent; however, numerous controlled studies have shown an improvement in anxiety and depression scores in those taking isotretinoin.
2. There is no association between IBD and isotretinoin use. Only one study showed a significantly increased risk of UC. When considering using isotretinoin in a patient with IBD or with a strong family history, consider involving a gastroenterologist.



Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo).

## Perioral Dermatitis

### Clinical Presentation

- discrete erythematous micropapules that often become confluent, forming inflammatory plaques on perioral, perinasal and periorbital skin
- commonly symmetrical, rim of sparing around vermillion border of lips
- aggravated by topical glucocorticoids

### Epidemiology

- 15-40 yr old, occasionally in younger children
- predominantly females

### Differential Diagnosis

- contact dermatitis, rosacea, acne vulgaris



## Management

- avoid all topical steroids
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid
- systemic: tetracycline family antibiotic (utilized for its anti-inflammatory properties)

## Rosacea

### Clinical Presentation

- dome-shaped papules ± pustules
- flushing, non-transient erythema and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks and chin (see Figure 3); rarely on scalp, neck and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, caffeine, spices (triggers of vasodilation)
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration and lymphedema in the skin can develop
- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: blepharoconjunctivitis, keratitis, iritis

### Pathophysiology

- unknown

### Epidemiology

- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 yr old; F>M

### Differential Diagnosis

- acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis

### Management

- trigger avoidance is key to long term management
- avoid topical corticosteroids
- make-up to mask erythema
- telangiectasia: treated by physical ablation; electrical hyfrecators, vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; paring, electrosurgery, cryotherapy, laser therapy (CO<sub>2</sub>, argon, Nd:YAG)
- early diagnosis and prompt treatment are recommended to prevent worsening

Table 9. Specific Rosacea Treatments

1st Line	2nd Line	3rd Line
Oral tetracyclines (250-500 mg PO bid)	Topical clindamycin	Oral retinoids
Topical metronidazole	Topical erythromycin 2% solution	Topical sulfur
Oral erythromycin (250-500 mg PO bid)	Topical benzoyl peroxide	
Topical azelaic acid	Oral metronidazole	
	Ampicillin	

## Dermatitis (Eczema)

### Definition

- inflammation of the skin

### Clinical Presentation

- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting
- chronic dermatitis: lichenification, xerosis, fissuring

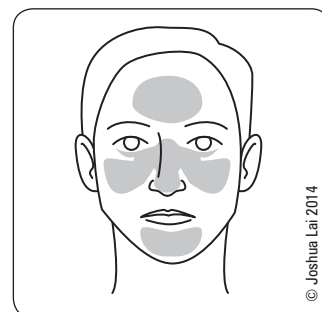


Figure 3. Rosacea distribution



Rosacea can be differentiated from acne by the absence of comedones, a predilection for the central face and symptoms of flushing.



### Guidelines for the Diagnosis of Rosacea

*J Am Acad Dermatol* 2002;46:584-7

Presence of one or more of the following primary features:

- Flushing (transient erythema)
- Nontransient erythema
- Papules and pustules
- Telangiectasia

May include one or more of the following secondary features:

- Burning or stinging
- Dry appearance
- Edema
- Phymatous changes
- Ocular manifestations
- Peripheral location



### Subtypes and Variants of Rosacea and Their Characteristics

N.B. the subtypes can all coexist and can be seen on a spectrum of severity

#### SUBTYPE

- **Erythromatotelangiectatic**
  - Flushing, persistent central facial erythema ± telangiectasia
- **Papulopustular**
  - Persistent central facial erythema
  - Transient central facial papules or pustules or both
- **Phymatous**
  - Thickening skin, irregular surface nodularities and enlargement
  - Nose most commonly, rarely occurs elsewhere (chin, forehead, cheeks or ears)
- **Ocular**
  - Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema

#### VARIANT

- **Granulomatous**
  - Noninflammatory, hard, brown, yellow, or red cutaneous papules or nodules of uniform size

## Asteatotic Dermatitis

### Clinical Presentation

- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (aka “winter itch”) but starts in the fall
- shins predominate, looks like a “dried river bed”

### Management

- skin rehydration with moisturizing routine
- ± mild corticosteroid creams

## Atopic Dermatitis

### Clinical Presentation

- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution
  - infant (onset at 2-6 mo old): face, scalp, extensor surfaces
  - childhood (>18 mo): flexural surfaces, especially antecubital fossae, popliteal fossae, and neck
  - adult: hands, feet, flexures, wrists, face, forehead, eyelids, neck
- inflammation, lichenification, excoriations are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with
  - keratosis pilaris (hyperkeratosis of hair follicles, “chicken skin”)
  - xerosis
  - occupational hand dryness

### Epidemiology

- frequently affects infants, children, and young adults
- almost 15% of children in developed countries under the age of 5 are affected
- associated with personal or family history of atopy (asthma, hay fever, anaphylaxis, eosinophilia)
- polygenic inheritance: one parent >60% chance for child; two parents >80% chance for child
- childhood onset and hereditary forms may be associated with null mutations in the protein filaggrin
- the earlier the onset, the more severe and persistent the disease
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

### Pathophysiology

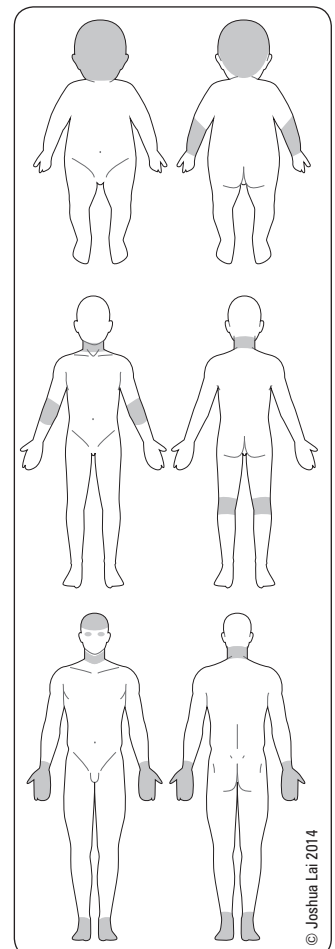
- a T-cell driven process with epidermal barrier dysfunction

### Investigations

- clinical diagnosis
- consider: skin biopsy, immunoglobulin serum levels (often elevated serum IgE level), patch testing, and skin prick tests

### Management

- goal: reduce signs and symptoms, prevent or reduce recurrences/flare
- better outcome (e.g. less flare-ups, modified course of disease) if diagnosis made early and treatment plan individualized
- avoid triggers of AD
- **enhance barrier function of the skin**
  - regular application of moisturizers
  - emollients hydrate the skin and reduce pruritus
  - twice daily application is recommended even in absence of symptoms, especially after bathing or swimming
  - bathing promotes hydration when followed by the application of moisturizers to the skin followed by occlusives (e.g. petroleum jelly)
- **anti-inflammatory therapies**
  - topical corticosteroids
    - effective, rapid symptomatic relief of acute flares
    - best applied immediately after bathing
    - control inflammation with a potent topical steroid; a milder one following resolution of acute flare
    - systemic immunosuppression may be needed in severe cases
    - flares may respond to systemic anti-staphylococcal therapy
    - side effects: skin atrophy, purpura, striae, steroid acne, perioral dermatitis, and glaucoma when used around the eyes



**Figure 4. Atopic dermatitis distribution**



#### Triggers for Atopic Dermatitis

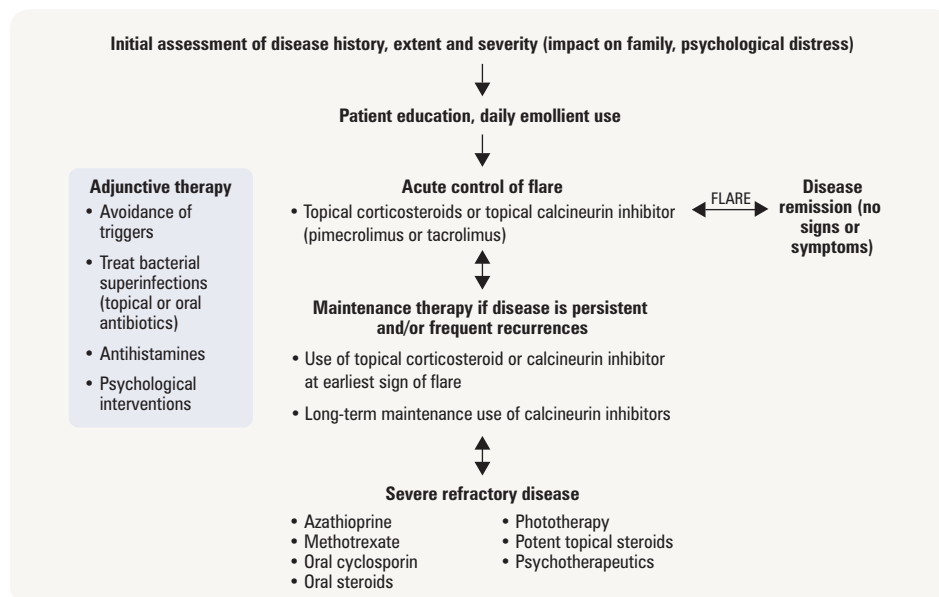
- Irritants (detergents, solvents, clothing, water hardness)
- Contact allergens
- Environmental aeroallergens (dust mites)
- Inappropriate bathing habits (long hot showers)
- Sweating
- Microbes (*S. aureus*)
- Stress

**B. topical immunomodulators**

- long-term management
- calcineurin inhibitors include pimecrolimus (Elidel®), tacrolimus (Protopic®)
- side effects: skin burning, transient irritation
- advantages of immunomodulators over long-term corticosteroid use
  - ♦ rapid, sustained effect in controlling pruritus
  - ♦ no skin atrophy
  - ♦ safe for the face and neck

**Complications**

- infections
  - treatment of infections
    - ♦ topical mupirocin or fusidic acid (Canada only, not available in US)
    - ♦ oral antibiotics (e.g. cloxacillin, cephalexin) for widespread *S. aureus* infections

**Figure 5. Atopic dermatitis treatment algorithm**

Adapted from: Ellis C, et al. ICCAD II Faculty. International Consensus Conference on Atopic Dermatitis II (ICCAD II): clinical update and current treatment strategies. *Br J Dermatol* 2003;148(Suppl 63):3-10

**The Diagnostic Value of Atopy Patch Testing and Prick Testing in Atopic Dermatitis: Facts and Controversies**

*Clin Dermatol* 2010;28:38-44

**Study:** Systematic review.

**Conclusions:**

Use of the atopy patch test (APT) is controversial:

- There is no gold standard for aeroallergen provocation, so APT is used without comparison to another method.
- APT findings are not consistent among children with atopic dermatitis.

APT may be valuable:

- May provide diagnostic information and may aid clinical decision making regarding the use of IGE-mediated sensitizations

Future research is needed:

- Need standardized provocation and avoidance testing to determine the clinical relevance of obtaining a positive APT result

**Top Ten Allergens as Identified by The North American Contact Dermatitis Group**

Test Substance	Allergic Reactions (%)	Common Uses
Nickel sulfate	14.2	Found in some jewelry, belt buckles
Neomycin sulfate	13.1	Most commonly used topical antibiotic
Balsam of Peru	11.8	Fragrance material
Fragrance mix	11.7	A mix of eight different fragrance components which was developed to allow for allergen testing in cosmetics
Thimerosal	10.9	A common preservative that is used in vaccines, contact lens solution, cosmetics
Sodium gold	9.5	Used in jewellery, dentistry, thiosulfate electronics
Formaldehyde	9.3	A colourless gas found in many workplaces, cosmetics, medications, textiles, resins, plastic bottles
Quaternium-15	9.0	A component in many shampoos, moisturizers, conditioners and soaps
Cobalt chloride	9.0	A hard metal found in cosmetics, jewellery, buttons, tools
Bacitracin	8.7	A topical antibiotic – one of the main ingredients in Polysporin®

## Contact Dermatitis

**Clinical Presentation**

- cutaneous inflammation caused by an external agent(s)

**Table 10. Contact Dermatitis**

	Irritant Contact Dermatitis	Allergic Contact Dermatitis
<b>Mechanism of Reaction</b>	Toxic injury to skin; non-immune mechanism	Cell-mediated delayed (Type IV) hypersensitivity reaction (see <a href="#">Rheumatology</a> , RH2)
<b>Type of Reaction</b>	Erythema, dryness, fine scale, burning Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure) Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common	Erythema with a papulovesicular eruption, swelling, pruritus
<b>Frequency of Contact Dermatitis</b>	Majority; will occur in anyone given sufficient concentration of irritants	Minority; patient acquires susceptibility to allergen that persists indefinitely
<b>Distribution</b>	Palmar surface of hand usually involved	Dorsum of hand usually involved; often discrete area of skin involvement
<b>Examples</b>	Soaps, weak alkali, detergents, organic solvents, alcohol, oils	(See sidebar) Many allergens are irritants, so may coincide with irritant dermatitis
<b>Management</b>	Avoidance of irritants Wet compresses with Burow's solution Barrier moisturizers Topical/oral steroids	Patch testing to determine specific allergen Avoid allergen and its cross-reactants Wet compresses soaked in Burow's solution (drying agent) Steroid cream (e.g. hydrocortisone 1%, betamethasone valerate 0.05% or 0.1% cream; bid) Systemic steroids pm (prednisone 1 mg/kg, taper over 2 wk)

## Dyshidrotic Dermatitis

### Clinical Presentation

- “tapioca pudding” papulovesicular dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infection common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

### Pathophysiology

- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate the dermatitis

### Management

- topical: high potency corticosteroid with plastic cling wrap occlusion to increase penetration
- intralesional triamcinolone injection
- systemic:
  - prednisone in severe cases
  - antibiotics for secondary *S. aureus* infection

## Nummular Dermatitis

### Clinical Presentation

- annular, coin-shaped, pruritic, dry, scaly, erythematous plaques, can become lichenified
- often associated with atopic and dyshidrotic dermatitis
- secondary infection common

### Management

- moisturization
- mid to high potency corticosteroid ointment bid

## Seborrheic Dermatitis

### Clinical Presentation

- greasy, erythematous, yellow, scaling, minimally elevated papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: cause of “cradle cap”
- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

### Pathophysiology

- possible etiologic association with *Malassezia* spp. (yeast)

### Epidemiology

- common in infants and at puberty
- increased incidence and severity in immunocompromised patients (e.g. HIV)
- in adults, can cause dandruff (pityriasis sicca)

### Management

- face: ketoconazole (Nizoral®) cream daily or bid + mild steroid cream daily or bid
- scalp: salicylic acid in olive oil or Derma-Smoother FS® lotion (peanut oil, mineral oil, fluocinolone acetonide 0.01%) to remove dense scales, 2% ketoconazole shampoo (Nizoral®), ciclopirox (Stieprox®) shampoo, selenium sulfide (e.g. Selsun®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)

## Stasis Dermatitis

### Clinical Presentation

- persistent inflammation of the lower legs with erythema, xerosis, scaling, and brownish pigmentation in late stages
- associated with venous insufficiency

### Management

- compression stockings
- rest and elevate legs (above the level of the heart)
- moisturizer to treat xerosis
- mid-high potency topical corticosteroids to control inflammation

### Complications

- ulceration (common at medial malleolus), secondary bacterial infections

## Lichen Simplex Chronicus

### Clinical Presentation

- chronic dermatitis resulting from continued rubbing/scratching of skin → lichenified skin
- may develop secondarily to another pruritic skin disease

### Management

- treat pruritus to break the itch-scratch cycle: antihistamines, topical antipruritics
- topical high-potency corticosteroids

## Papulosquamous Diseases

### Lichen Planus

#### Clinical Presentation

- acute or chronic inflammation of mucous membranes or skin characterized by violaceous papules, especially on flexural surfaces
- small, polygonal, flat-topped, shiny, violet papules; resolves into hyperpigmented macules
- sites: wrists, ankles, mucous membranes in 60% (mouth, vulva, glans), nails, scalp
- distribution: symmetrical and bilateral
- Wickham's striae: reticulate white-grey lines over surface; pathognomonic
- mucous membrane lesions: lacy, whitish reticular network, milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging; dystrophic; pterygium formation
- scalp: scarring alopecia with perifollicular hyperkeratosis
- spontaneously resolves but may last for weeks, months or years (mouth and skin lesions)
- rarely associated with hepatitis C
- Koebner phenomenon
- may be triggered by severe emotional stress

#### Management

- topical corticosteroids with occlusion or intradermal steroid injections
- short courses of oral prednisone (rarely)
- photochemotherapy for generalized or resistant cases
- oral retinoids for erosive lichen planus in mouth
- systemic immunosuppression/modulation e.g. azathioprine, methotrexate, cyclosporine, metronidazole



#### The 6 Ps of Lichen Planus

Purple  
Pruritic  
Polygonal  
Peripheral  
Papules  
Penis (i.e. mucosa)

### Pityriasis Rosea



#### Clinical Presentation

- acute, self-limiting eruption characterized by red, oval plaques/patches with central scale that does not extend to edge of lesion
- long axis of lesions follows skin tension lines (aka Langer's Lines) parallel to ribs producing "Christmas tree" pattern on back
- varied degree of pruritus
- most start with a "herald" patch which precedes other lesions by 1-2 wk
- sites: trunk, proximal aspects of arms and legs

## Etiology

- suspected HHV7

## Management

- none required; clears spontaneously in 6-12 wk, reassurance
- topical corticosteroids when post-inflammatory pigmentation is a concern or if patient is uncomfortable
- oral erythromycin or oral acyclovir may expedite healing

# Psoriasis

## Classification

1. plaque psoriasis
2. guttate psoriasis
3. erythrodermic psoriasis
4. pustular psoriasis
5. psoriatic arthritis

## Differential Diagnosis

- atopic dermatitis, mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea

## Diagnosis

- usually clinical, biopsy to confirm
- psoriasis area and severity index (PASI)
  - score is based on: percentage of surface area involved and the severity of symptoms (erythema, infiltration, desquamation)

## 1. PLAQUE PSORIASIS

### Clinical Presentation

- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- often worse in winter (lack of sun and humidity)
- Koebner phenomenon
- Auspitz sign: bleeds from minute points when scale is removed
- usually non-pruritic
- exacerbating factors: drugs (lithium, ethanol, chloroquine,  $\beta$ -blockers), stress
- sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

### Pathophysiology

- decreased epidermal transit time from stratum basale to stratum corneum
- shortened cell cycle of psoriatic compared to normal skin
- Th1-mediated inflammatory response

### Management

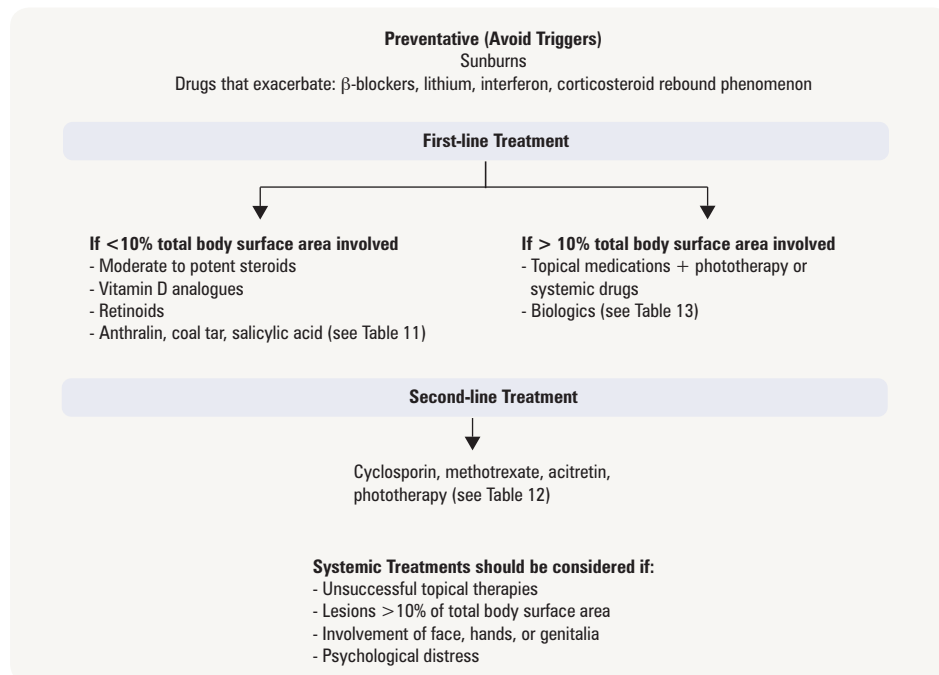


Figure 6. Management of plaque psoriasis



### PSORIASIS: Presentation and Pathophysiology

Pink papules/Plaques/Pinpoint bleeding (Auspitz sign)/Physical injury (Koebner phenomenon)  
 Silver scale/Sharp margins  
 Onycholysis/Oil spots  
 Rete Ridges with Regular elongation  
 Itching  
 Arthritis/Abscess (Munro)/Autoimmune  
 Stratum corneum with nuclei  
 Immunologic  
 Stratum granulosum absent



### PSORIASIS: Triggers

- Physical trauma (Koebner phenomenon)
- Infections (acute streptococcal infection precipitates guttate psoriasis)
- Stress (can be a major factor in flares)
- Drugs (systemic glucocorticoids, oral lithium, antimalarial drugs, interferon)
- Alcohol ingestion



**Table 11. Topical Treatment of Psoriasis**

Treatment	Mechanism	Comments
Lubricants	Reduce fissure formation	Petrolatum is effective
Salicylic acid 1-12%	Remove scales	
Tar (LCD: Liquor carbonis detergens) 20% coal tar solution	Inhibits DNA synthesis, increases cell turnover	Poor long term compliance
Calcipotriene /calitriol (Dovonex <sup>®</sup> , Vectical <sup>®</sup> )	Binds to skin 1,25-dihydroxyvitamin D3 to inhibit keratinocyte proliferation	Can be used on face and skin folds
Betamethasone + calcipotriene (Dovobet <sup>®</sup> , Taclonex <sup>®</sup> )	See above	Sold as Dovobet <sup>®</sup> in Canada and Europe, sold as Taclonex <sup>®</sup> in US
Corticosteroid ointment	Reduce scaling and thickness	Use appropriate potency steroid in different areas for degree of psoriasis
Tazarotene (Tazorac <sup>®</sup> ) (gel/cream)	Retinoid derivative, decreased scaling	Use on nails

**Table 12. Systemic Treatment of Psoriasis**

Treatment	Adverse Effects
Methotrexate	Bone marrow toxicity, hepatic cirrhosis
PUVA	Pruritus, burning, cataracts, skin cancer
Acitretin	Alopecia, cheilitis, teratogenicity, epistaxis, xerosis, hypertriglyceridemia
Cyclosporine	Renal toxicity, hypertension, immunosuppression
UVB and "Narrow band" UVB (311-312 nm)	Well tolerated

**Table 13. Biologics Approved in Canada**

Treatment	Route	Dosing Schedule	Effectiveness	Action
etanercept (Enbrel <sup>®</sup> )*	SC	Twice weekly initially	+++	Anti-TNF
adalimumab (Humira <sup>®</sup> )*	SC	Once every 2 wk	++++	Anti-TNF
infliximab (Remicade <sup>®</sup> )*	IV	~Every 2 mo	+++++	Anti-TNF
ustekinumab (Stelara <sup>®</sup> )	SC	Every 12 wk during maintenance	++++	Anti-IL 12/23

\*Can also be used to treat psoriatic arthritis

## 2. GUTTATE PSORIASIS ("DROP-LIKE")

### Clinical Presentation

- discrete, scattered salmon-pink scaling papules
- sites: generalized, sparing palms and soles
- often antecedent streptococcal pharyngitis

### Management

- UVB phototherapy, sunlight, lubricants
- penicillin V or erythromycin if Group A  $\beta$ -hemolytic Streptococcus on throat culture

## 3. ERYTHRODERMIC PSORIASIS

### Clinical Presentation

- generalized erythema with fine desquamative scale on surface
- associated symptoms: arthralgia, severe pruritus
- may present in patient with previous mild plaque psoriasis
- aggravating factors: lithium,  $\beta$ -blockers, NSAIDs, antimalarials, phototoxic reaction, infection

### Management

- hospitalization, bed rest, IV fluids, monitor fluid and electrolytes
- treat underlying aggravating condition, sun avoidance
- methotrexate, cyclosporine, UV, oral retinoids, biologics



#### Topical Treatments for Chronic Plaque Psoriasis

Cochrane DB Syst Rev 2009;2:CD005028

**Study:** Systematic review of randomized trials comparing treatments against placebo or against vitamin D.

**Patients:** 21,448 patients with chronic plaque psoriasis.

**Intervention:** Corticosteroids, dithranol, tarazotene, salicylic acid, retinoids, methotrexate, macrolactams, vitamin D, and vitamin D + corticosteroids.

**Outcome:** Investigator assessment of overall global improvement. Total severity scores. Psoriasis area and severity index. Patient assessment of overall global improvement.

**Results:** Corticosteroids, vitamin D, dithranol, and tazarotene performed better than placebo alone. A combination of corticosteroids and vitamin D were better than either vitamin D or corticosteroids alone.



#### Calcipotriol is a vitamin D derivative

**Dovobet<sup>®</sup>** = calcipotriene combined with betamethasone dipropionate and is considered to be the most potent topical psoriatic therapy.



#### Efficacy and Tolerability of Biologic and Nonbiologic Systemic Treatments for Moderate-to-Severe Psoriasis: Meta-analysis of randomized Controlled Trials

Br J Derm 2008;159:513-526

**Study:** Meta-analysis of 16 double-blind placebo-controlled trials.

**Patients:** Patients with moderate to severe psoriasis (PASI cutoff of 7).

**Intervention:** Treatment with fumaric acid ester, cyclosporine, infliximab, etanercept, efalizumab, or adalimumab vs. placebo.

**Main Outcome:** Proportion of study subjects with at least a 75% reduction in PASI score.

**Results:** The highest efficacy was observed with biologics, infliximab (Risk Difference (RD) = 77%), followed by Adalimumab (RD = 64%). No conclusions could be made about long-term safety of biologic treatments.



#### Mechanism of Biologics

"-mab" = monoclonal antibody  
"-cept" = receptor

#### 4. PUSTULAR PSORIASIS



##### Clinical Presentation

- sudden onset of erythematous macules and papules which evolve rapidly into pustules, very painful
- can be generalized or localized to palms/soles
- patient usually has history of psoriasis; may occur with sudden withdrawal from steroid therapy

##### Management

- methotrexate, oral retinoids, biologics

#### 5. PSORIATIC ARTHRITIS

- 5 categories
  - asymmetric oligoarthritis
  - DIP joint involvement (predominant)
  - rheumatoid pattern (symmetric polyarthropathy)
  - psoriatic arthritis mutilans (most severe form)
  - predominant spondylitis or sacroiliitis
- see [Rheumatology](#), RH23



## Vesiculobullous Diseases

### Bullous Pemphigoid

##### Clinical Presentation

- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth (33%)

##### Pathophysiology

- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leads to subepidermal bullae

##### Epidemiology

- 60-80 yr old
- there are case reports of association with internal malignancy, but this is exceedingly rare

##### Investigations

- immunofluorescence shows linear deposition of IgG and C3 along the basement membrane
- anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

##### Prognosis

- generalized bullous eruption heals without scarring
- rarely fatal

##### Management

- prednisone ± steroid-sparing agents (e.g. azathioprine, methotrexate)
- topical potent steroids (clobetasol) may be as effective as systemic steroids
- tetracycline ± nicotinamide is effective for some cases
- dapsone for milder cases



##### Pemphigus Vulgaris vs. Bullous Pemphigoid

Vulgaris = Superficial, intraepidermal, flaccid lesions  
Pemphigoid = Deeper, tense lesions at the dermal-epidermal junction

### Pemphigus Vulgaris

##### Clinical Presentation

- autoimmune blistering disease characterized by flaccid, non-pruritic epidermal bullae/vesicles on an erythematous or normal skin base
- may present with erosions and secondary bacterial infection
- sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
- Nikolsky's sign: sliding or rubbing pressure on skin → separation of epidermis
- Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

##### Pathophysiology

- IgG produced against epidermal desmoglein-1 and -3 leads to intraepidermal bullae

##### Epidemiology

- 40-60 yr old, higher prevalence in Jewish, Mediterranean, Asian populations
- paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine



##### Pemphigus Foliaceus

An autoimmune intraepidermal blistering disease that is more superficial than pemphigus vulgaris due to antibodies against desmoglein-1, a transmembrane adhesion molecule. Appears as crusted patches and erosions which can initially be managed with topical steroids if localized. Active widespread disease is treated like pemphigus vulgaris.

### Investigations

- immunofluorescence: shows IgG and C3 deposition intraepidermally
- circulating serum anti-desmoglein IgG antibodies

### Prognosis and Clinical Course

- begins with mouth lesions, followed by skin lesions
- first localized (6-12 mo) then generalized
- lesions heal with hyperpigmentation but no scar
- may be fatal unless treated with immunosuppressive agents

### Management

- prednisone 1-3 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper
- steroid-sparing agents: azathioprine, methotrexate, gold, cyclophosphamide, cyclosporine, intravenous immunoglobulin (IVIG), mycophenolate mofetil, rituximab
- plasmapheresis for acutely high antibody levels



#### Azathioprine

Thiopurine methyltransferase (TPMT) levels should be measured before starting therapy. Individuals with low enzyme activity will experience greater immunosuppression.

**Table 14. Summary of Vesiculobullous Diseases**

	<b>Bullous Pemphigoid</b>	<b>Dermatitis Herpetiformis</b>	<b>Pemphigus Vulgaris</b>
<b>Antibody</b>	IgG	IgA	IgG
<b>Site</b>	Basement membrane	Dermal	Intraepidermal
<b>Infiltrate</b>	Eosinophils	Neutrophils	Eosinophils and neutrophils
<b>Management</b>	Systemic steroids Immunosuppressive agents Tetracycline Clobetasol cream	Gluten-free diet Dapsone	High dose steroids Immunosuppressive agent (e.g. Imuran®, mycophenolic acid)
<b>Association</b>	Malignancy (rarely)	Gluten enteropathy Thyroid disease Intestinal lymphoma	Malignancy with paraneoplastic pemphigus

## Dermatitis Herpetiformis

### Clinical Presentation

- grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging
- almost always excoriated, rarely seen as blisters
- lesions grouped, bilaterally symmetrical
- sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

### Pathophysiology

- 90% have HLA B8, DR3, DQWZ
- 90% associated with an often subclinical gluten-sensitive enteropathy (celiac)
- 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

### Epidemiology

- 20-60 yr old, M:F = 2:1

### Management

- dapsone for pruritus
- gluten-free diet for life

## Porphyria Cutanea Tarda

### Clinical Presentation

- tense vesicles/bullae in photoexposed areas subjected to trauma
- facial hypertrichosis, brown hypermelanosis vesicles, and bullae in photodistribution (dorsum of hands and feet)
- sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

### Pathophysiology

- autosomal dominant or sporadic skin disorder associated with the presence of excess heme precursors
- associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

### Epidemiology

- 30-40 yr old, M>F

### Investigations

- urine + 5% HCl shows orange-red fluorescence under Wood's lamp (UV rays)
- 24 hour urine for uroporphyrins (elevated)
- stool contains elevated coproporphyrins
- immunofluorescence shows IgE at dermal-epidermal junctions

### Management

- discontinue aggravating substances (alcohol, estrogen therapy)
- phlebotomy to decrease body iron load
- low dose hydroxychloroquine

## Drug Eruptions

### Drug Hypersensitivity Syndrome

- fever followed by symmetrical bright red exanthematous eruption that may lead to internal organ involvement (hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
- classically occurs approximately 7-10 d after first exposure to the drug
- may be elevated incidence of similar reactions in siblings
- most common causes: sulfonamides, allopurinol, and anticonvulsants (phenytoin, phenobarbital, carbamazepine, lamotrigine)
- 10% mortality if severe, undiagnosed, and untreated



#### Drug Hypersensitivity Syndrome Triad

- Fever
- Exanthematous Eruption
- Internal Organ Involvement

### Erythema Multiforme (EM), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)



- disorders with varying presence of characteristic skin lesions, blistering and mucous membrane involvement

**Table 15. Comparison of Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis**

	Erythema Multiforme (EM)	Stevens-Johnson Syndrome (SJS)	Toxic Epidermal Necrolysis (TEN)
<b>Lesion</b>	Macules/papules with central vesicles Classic bull's-eye pattern of concentric light and dark rings (typical target lesions) Bilateral and symmetric All lesions appear within 72 h May show dermal edema Lesion "fixed" for at least 7 d	Cutaneous blistering with mucous membrane involvement (especially lips) "Atypical lesions": red circular patch with dark purple centre (aka targetoid) "Sicker" (high fever) Sheet-like epidermal detachment in <10% of BSA (Nikolsky sign)	Mucous membrane involvement, and severe blistering "Atypical lesions": 50% have no target lesions Diffuse erythema then necrosis and sheet-like epidermal detachment in >30% of BSA
<b>Sites</b>	Dorsa of hands and forearms Mucous membrane involvement (lips, tongue, buccal mucosa) is possible Extremities with face > trunk Involvement of palms and soles	Prominent face and trunk involvement Palms and soles may be spared	>30% BSA Nails may also shed
<b>Other Complications</b>	Burning and stinging Recurrences Secondary bacterial infection	Infection, scarring, contractures, eruptive nevocmelanocytic nevi, corneal scarring, blindness, phimosis and vaginal synechiae	Same as SJS's PLUS electrolyte imbalance, dehydration, tubular necrosis and acute kidney injury, epithelial erosions of trachea, death
<b>Constitutional Symptoms</b>	Weakness, malaise	Prodrome 1-14 d prior to eruption with fever and flu-like illness	High fever >38°C
<b>Etiology</b>	Infection: HSV, or <i>Mycoplasma pneumoniae</i>	Frequently drug-related (NSAIDs, anticonvulsants, sulfonamides, penicillins) Occurs up to 1-3 wk after drug exposure with more rapid onset upon rechallenge	Same as SJS
<b>Differential Diagnosis</b>	Urticaria, granuloma annulare, mycosis fungoides, vasculitis	Scarlet fever, phototoxic, eruption, GVHD, SSSS, exfoliative dermatitis, Kawasaki disease, paraneoplastic pemphigus	Same as SJS
<b>Course and Prognosis</b>	Lesions last 2 wk and heal without complications	4-6 wk course 5% mortality	30% mortality due to fluid loss, regrowth of epidermis by 3 wk, secondary infection
<b>Management</b>	Symptomatic treatment (oral antihistamines, oral antacids) Corticosteroids in severely ill (controversial) Prophylactic oral acyclovir for 6-12 mo for HSV-associated EM with frequent recurrences	Prolonged hospitalization Withdraw suspect drug Intravenous fluids Infection prophylaxis Consider IVIG vs. cyclosporine (corticosteroids controversial)	As for Stevens-Johnson syndrome Admit to burn unit Debride frankly necrotic tissue Consider IVIG vs. cyclosporine

**Intravenous Immunoglobulin Use in Patients with Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome***Am J Clin Dermatol* 2006;7:359-d68**Study:** Systematic review of 17 articles

(retrospective cohort studies were most common, no RCTs).

**Patients:** Individuals with a diagnosis of SJS/TEN treated with IVIG.**Intervention:** Various doses and regimens of IVIG.**Outcomes:** Time to disease cessation, time to healing.**Results:** Eleven of 14 TEN studies reported positive results, while three studies did not observe a statistically significant improvement. Two of three SJS studies reported positive results, with one study observing no significant difference in mortality, or speed of healing.**Conclusion:** IVIG appears to have a positive impact on TEN/SJS but results cannot be statistically analyzed as a whole due to variability and inconsistency in data presented from each study. However, it is considered the gold standard treatment.

## Exanthematous Eruptions (Maculopapular Eruptions/Morbilliform)

- symmetrical, widespread, erythematous patches or plaques  $\pm$  scales
- the “classic” and most common adverse drug reaction
- often starts on trunk
- may progress to generalized exfoliative dermatitis especially if the drug is continued
- most common causes: penicillin, sulfonamides, phenytoin

## Fixed Drug Eruptions

- sharply demarcated erythematous oval patches on the skin or mucous membranes
  - sites: face, mucosa, genitalia, acral
  - reoccurs in same location upon subsequent exposure to the drug (fixed location)
- most common causes: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein

## Photosensitivity Eruptions

- phototoxic reaction: “an exaggerated sunburn” confined to sun-exposed areas
- photoallergic reaction: an eczematous eruption that may spread to areas not exposed to light
- most common causes: chlorpromazine, doxycycline, thiazide diuretics, procainamide

## Serum Sickness-Like Reaction

- a symmetric drug eruption resulting in fever, arthralgia, lymphadenopathy, and skin rash (urticaria)
- usually appears 5-10 d after drug exposure
- most common causes: cefaclor in kids; bupropion (Zyban®, Wellbutrin®) in adults

## Heritable Disorders

### Ichthyosis Vulgaris

#### Clinical Presentation

- generalized hyperkeratosis leading to dry skin
- genetic deficiency in filaggrin protein
- “fish-scale” appearance especially on extremities with sparing of flexural creases, palms and soles

#### Pathophysiology

- abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

#### Epidemiology

- 1:300 incidence
- autosomal dominant inheritance
- associated with atopic dermatitis and keratosis pilaris

#### Management

- immersion in bath and oils
- emollient or humectant creams, and creams or oils containing urea or  $\alpha$ - or  $\beta$ -hydroxy acids

## Neurofibromatosis (Type I; von Recklinghausen's Disease)

### Clinical Presentation

- diagnostic criteria includes 2 or more of the following:
  1. more than 5 café-au-lait patches >1.5 cm in an adult or more than 5 café-au-lait macules >0.5 cm in a child under age 5
  2. axillary or inguinal freckling
  3. iris hamartomas (Lisch nodules)
  4. optic gliomas
  5. neurofibromas
  6. distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)
  7. first degree relative with neurofibromatosis type 1
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see [Pediatrics](#), P91)



### Pathophysiology

- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence of neurofibromin (a tumour suppressor gene)

### Epidemiology

- incidence 1:3,000

### Management

- watch for brain tumors such as astrocytoma
- excise suspicious or painful lesions
- see [Pediatrics](#), P92



## Vitiligo

### Clinical Presentation

- primary pigmentary disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply margined white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

### Pathophysiology

- acquired autoimmune destruction of melanocytes

### Epidemiology

- 1% incidence, polygenic
- 30% with positive family history

### Investigations

- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison's disease, Type I DM
- Wood's lamp to detect lesions: illuminates UV light onto skin to detect patches of amelanosis

### Management

- sun avoidance and protection
- topical immunomodulator (i.e. tacrolimus, pimecrolimus) or a topical steroid
- PUVA or Narrow band UVB
- make-up
- "bleaching" normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation



#### Interventions for Vitiligo

*Cochrane DB Syst Rev* 2010;1:CD003263

**Study:** Systematic review of randomized controlled trials.

**Patients:** 3139 participants with vitiligo.

**Intervention:** Topical treatments, light therapies, oral treatments, surgical methods, and psychological therapies

**Outcome:** >75% repigmentation, adverse effects

**Results:** Moderate evidence exists for the use of topical corticosteroids to induce repigmentation. However, adverse effects are observed with long-term use. Topical use of non-steroidal immunomodulators (i.e. tacrolimus), especially in combination with light therapies, has also been shown to induce repigmentation. However, long-term use may theoretically increase the risk for skin cancer. In general, combination therapy including some form of light therapy had the most significant improvement. Sustained repigmentation (>2 yr) has not been reported and thus results should be treated with caution.



# Infections



## Bacterial Infections

- often involve the epidermis, dermis, hair follicles or periungual region  $\pm$  systemic

### EPIDERMIS



### IMPETIGO



#### Clinical Presentation

- acute purulent infection which appears vesicular; progresses to golden yellow “honey-crusted” lesions surrounded by erythema
- can present with bullae
- sites: commonly face, arms, legs and buttocks

#### Etiology

- GAS, *S. aureus*, or both

#### Epidemiology

- preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

#### Differential Diagnosis

- infected eczema, HSV, Varicella virus

#### Investigations

- Gram stain and culture of lesion fluid or biopsy

#### Management

- remove crusts, use saline compresses and topical antiseptic soaks bid
- topical antibacterials such as 2% mupirocin or fusidic acid (Canada only) tid; continue for 7-10 d after resolution
- systemic antibiotics such as cloxacillin or cephalexin for 7-10 d

### DERMIS

**Table 16. Comparison of Erysipelas and Cellulitis**

	Erysipelas	Cellulitis
<b>Clinical Presentation</b>	Involves upper dermis Confluent, erythematous, sharp raised edge, warm plaque, well demarcated Very painful (“St. Anthony’s fire”) Sites: face and legs Systemic symptoms: fever, chills, headache, weakness (if present, sign of more serious infection)	Involves lower dermis/subcutaneous fat Unilateral erythematous flat lesion, often with vesicles poorly demarcated, not uniformly raised Tender Sites: commonly on legs Systemic symptoms (uncommon): fever, leukocytosis, lymphadenopathy
<b>Etiology</b>	GAS	GAS, <i>S. aureus</i> (large sized wounds), <i>H. influenzae</i> (periorbital), <i>Pasteurella multocida</i> (dog/cat bite)
<b>Complications</b>	Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy Spreads via lymphatics	Uncommon
<b>Differential Diagnosis</b>	DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis	Same as erysipelas
<b>Investigations</b>	Clinical diagnosis: rarely do skin/blood culture If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology	Same as erysipelas
<b>Management</b>	1st line: penicillin, cloxacillin or cefazolin 2nd line: clindamycin or cephalexin If allergic to penicillin, use erythromycin	1st line: cloxacillin or cefazolin/cephalexin 2nd line: erythromycin or clindamycin Children: cefuroxime If diabetes mellitus (foot infections): TMP/SMX and metronidazole



## COMMON HAIR FOLLICLE INFECTIONS

Table 17. Comparison of Superficial Folliculitis, Furuncles and Carbuncles

	Superficial Folliculitis	Furuncles (Boils)	Carbuncles
<b>Clinical Presentation</b>	Superficial infection of the hair follicle (versus pseudofolliculitis: inflammation of follicle due to friction, irritation, or occlusion) Acute lesion consists of a dome-shaped pustule at the mouth of hair follicle Pustule ruptures to form a small crust Sites: primarily scalp, shoulders, anterior chest, upper back, other hair-bearing areas	Red, hot, tender, inflammatory nodules with central yellowish point, which forms over summit and ruptures Involves subcutaneous tissue that arises from a hair follicle Sites: hair-bearing skin (thigh, neck, face, axillae, perineum, buttocks)	Deep-seated abscess formed by multiple coalescing furuncles Usually in areas of thicker skin Occasionally ulcerates Lesions drain through multiple openings to the surface Systemic symptoms may be associated
<b>Etiology</b>	Normal non-pathogenic bacteria ( <i>Staphylococcus</i> – most common; <i>Pseudomonas</i> – hot tub) <i>Pityrosporum</i>	<i>S. aureus</i>	<i>S. aureus</i>
<b>Management</b>	Antiseptic (Hibiclens®) Topical antibacterial (fusidic acid, mupirocin, or erythromycin) Oral cloxacillin for 7-10 d	Incise and drain large carbuncles to relieve pressure and pain If afebrile: hot wet packs, topical antibiotic If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&S) Cloxacillin for 1-2 wk (especially for lesions near external auditory canal/nose, with surrounding cellulitis, and not responsive to topical therapy)	Same as for furuncles

## Dermatophytoses



## Clinical Presentation

- infection of skin, hair and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

## Pathophysiology

- digestion of keratin by dermatophytes results in scaly skin, broken hairs, crumbling nails/onycholysis

## Etiology

- Trichophyton*, *Microsporum*, *Epidermophyton* species (*Pityrosporum* is a superficial yeast and not a dermatophyte)

## Investigations

- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia

## Management

- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type):
  - e.g. clotrimazole or terbinafine cream applied bid, until one week after complete resolution of lesions
- oral therapy is indicated for onychomycosis or tinea capitis:
  - e.g. terbinafine (Lamisil® – liver toxicity, CYP 2D6 inhibitor) or itraconazole (Sporanox® – CYP 3A4 inhibitor, liver toxicity)

Table 18. Different Manifestations of Dermatophyte Infection

	Clinical Presentation	Differential Diagnosis	Investigations	Management
<b>Tinea Capitis</b>	Round, scaly patches of alopecia, possibly with broken off hairs; pruritic Sites: scalp, eyelashes, and eyebrows; involving hair shafts and follicles Kerion (boggy, elevated, purulent inflamed nodule/plaque) may form secondary to infection by bacteria and result in scarring May have occipital lymphadenopathy Affects children (mainly black), immunocompromised adults Very contagious and may be transmitted from barber, hats, theatre seats, pets	Alopecia areata, psoriasis, seborrheic dermatitis, trichotillomania	Wood's light examination of hair: green fluorescence only for <i>Microsporum</i> infection Culture of scales/hair shaft Microscopic examination of KOH preparation of scales or hair shafts	Terbinafine (Lamisil®) x 4 wk NB: oral agents are required to penetrate the hair root where dermatophyte resides Adjunctive antifungal shampoos or lotions may be helpful, and may prevent spread (e.g. selenium sulfide, ketoconazole, ciclopirox)
<b>Tinea Corporis (Ringworm)</b>	Pruritic, scaly, round/oval plaque with active erythematous margin and central clearing Site: trunk, limbs, face	Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis	Microscopic examinations of KOH prep of scales shows hyphae Culture of scales	Topicals: 1% clotrimazole, 2% ketoconazole 2% miconazole, terbinafine or ciclopirox olamine cream bid for 2-4 wk Oral terbinafine, or itraconazole, or fluconazole, or ketoconazole if extensive



**Table 18. Different Manifestations of Dermatophyte Infection** (continued)

	Clinical Presentation	Differential Diagnosis	Investigations	Management
<b>Tinea Cruris</b> (“Jock Itch”)	Scaly patch/plaque with a well-defined, curved border and central clearing Pruritic, erythematous, dry/macerated Site: medial thigh	Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma	Same as for tinea corporis	Same as for tinea corporis
<b>Tinea Pedis</b> (Athlete’s Foot)	Pruritic scaling and/or maceration of the web spaces and powdery scaling of soles Acute infection: interdigital (esp. 4th web space) red/white scales, vesicles, bullae, often with maceration Secondary bacterial infection may occur Chronic: non-pruritic, pink, scaling keratosis on soles and sides of feet May present as flare-up of chronic tinea pedis Predisposing factors: heat, humidity, occlusive footwear	Atopic dermatitis, contact dermatitis, dyshidrotic dermatitis, erythrasma, intertrigo, inverse psoriasis	Same as for tinea corporis	Same as for tinea corporis
<b>Tinea Manuum</b>	Primary fungal infection of the hand is rare; usually associated with tinea pedis Acute: blisters at edge of red areas on hands Chronic: single dry scaly patch	Atopic dermatitis, contact dermatitis, granuloma annulare, psoriasis	Same as for tinea corporis	Same as for tinea corporis
<b>Tinea Unguium</b> (Onychomycosis)	Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris Toenail infections usually precede fingernail infections <i>T. rubrum</i> (90% of all toenail infections)	Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophies, bacterial infections	Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae Culture of subungual scraping or nail clippings on Sabouraud’s agar PAS stain of nail clipping by pathology	Terbinafine (Lamisil®) (6 wk for fingernails, 12 wk for toenails) Itraconazole (Sporanox®) 7 d on, 3 wk off (2 pulses for fingernails, 3 pulses for toenails) Topical: ciclopirox (Penlac®); nail laquer (often ineffective)

## Parasitic Infections



### SCABIES



#### Clinical Presentation

- a transmissible parasitic skin infection due to *Sarcoptes scabiei*, a mite, characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- primary lesion: superficial linear burrows; inflammatory papules and nodules in the axilla and groin
- secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- sites: axillae, groin, buttocks, hands/feet (especially web spaces), sparing of head and neck (except in infants)

#### Pathogenesis

- scabies mite remains alive 2-3 d on clothing/sheets
- incubation of 1 mo, then pruritus begins
- re-infection followed by hypersensitivity in 24 h

#### Etiology

- Sarcoptes scabiei*
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

#### Differential Diagnosis

- asteatotic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)

#### Investigations

- microscopic examination of root and content of burrow and mineral oil mount for mite, eggs, feces

#### Management

- bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment 7 d after first treatment)
- change underwear and linens; wash with detergent in hot water cycle then machine dry
- treat family and close contacts
- pruritus may persist for 2-3 wk after effective treatment due to prolonged hypersensitivity reaction
- mid potency topical steroids and antihistamines for symptom management

## LICE (PEDICULOSIS)

### Clinical Presentation

- intensely pruritic red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs
  - red excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs
  - excoriations
- body lice: nits and lice in seams of clothing
  - excoriations and secondary infection mainly on shoulders, belt-line and buttocks

### Differential Diagnosis

- bacterial infection of scalp, seborrheic dermatitis

### Management

- permethrin 1% (Nix® cream rinse) (ovicidal) or permethrin 1% (RC & Cor®, Kwellada-P® shampoo)
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 d after first treatment
- shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle then machine dry

## BED BUGS (HEMIPTERA)

- thought to have been eradicated in developed world during 1940s
- increasing in prevalence since 1995

### Clinical Presentation

- burning wheals, turning to firm papules, often in groups of three – “breakfast, lunch and dinner” in areas with easy access (face, neck, arms, legs, hands)

### Etiology

- caused by *Cimex lectularius*, a small insect that feeds mainly at night
- during day bedbugs hide in crevices in walls and furniture

### Differential Diagnosis

- dermatitis herpetiformis, drug eruptions, ecthyma, other insect bites, scabies

### Management

- professional fumigation of home
- topical steroids and oral H1-antagonists for symptomatic relief
- definitive treatment is removal of clutter in home and application of insecticides to walls and furniture

## Viral Infections



### HERPES SIMPLEX



#### Clinical Presentation

- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- **primary**
  - children and young adults
  - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - followed by antibody formation and latency of virus in dorsal nerve root ganglion
- **secondary**
  - recurrent form seen in adults; much more common than primary
  - prodrome: tingling, pruritus, pain
  - triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- **potential complications**
  - dendritic corneal ulcer
  - EM
  - herpes simplex encephalitis (infants at risk)
  - HSV infection on atopic dermatitis causing Kaposi's varicelliform eruption (eczema herpeticum)
- two biologically and immunologically different subtypes: HSV-1 and HSV-2

**HSV-1**

- typically “cold sores” (grouped vesicles at the mucocutaneous junction which quickly burst)
- recurrent on face, lips and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)

**Management**

- treat during prodrome to prevent vesicle formation
- topical antiviral (Zovirax®) cream, apply 5-6x/d x 4-7 d for facial/genital lesions
- oral antivirals are far more effective and have an easier dosing schedule

**HSV-2**

- sexually transmitted; incubation 2-20 d
- gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
- vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
- urethritis: watery discharge in males
- recurrent on vulva, vagina, penis for 5-7 d
- diagnosis
  - negative dark field, negative serology for syphilis, negative bacterial cultures
  - Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
  - tissue culture and electron microscopy of vesicular fluid
  - skin biopsy
  - antibody titres increase one week after primary infection only (no increase with recurrent lesions)
- ddx of genital ulcers: *Candida* balanitis, chancroid, syphilitic chancres

**Management**

- rupture vesicle with sterile needle if you wish to culture it
- wet dressing with aluminum subacetate solution, Burow's compression, or betadine solution
- 1st episode: acyclovir 200 mg PO 5 times a day x 10 d
  - maintenance: acyclovir 400 mg PO bid
- famciclovir and valacyclovir may be substituted and have better enteric absorption and less frequent dosing
- in case of herpes genitalis, look for and treat any other sexually-transmitted infections
- for active lesions in pregnancy, see [Obstetrics](#), OB21

**HERPES ZOSTER (SHINGLES)****Clinical Presentation**

- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last days – weeks
- pain is pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Hutchinson's sign: involvement of tip of nose suggests eye involvement
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV

**Etiology**

- caused by reactivation of VZV
- risk factors: immunosuppression, old age, occasionally associated with hematologic malignancy

**Differential Diagnosis**

- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)

**Management**

- compress with normal saline, Burow's, or betadine solution
- analgesics (NSAIDs, amitriptyline)
- famciclovir or valacyclovir or acyclovir for 7 d; must initiate within 72 h to be of benefit
- gabapentin 300-600 mg PO tid for post-herpetic neuralgia

**MOLLUSCUM CONTAGIOSUM****Clinical Presentation**

- discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus [*Molluscum contagiosum* virus (MCV)]
- sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

**Etiology**

- MCV is spread via direct contact, auto-inoculation, sexual contact
- common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)



Both HSV-1 and HSV-2 can occur on face or genitalia.



Herpes Zoster typically involves a single dermatome; lesions rarely cross the midline.



**Management**

- topical cantharidin (a vesicant)
- cryotherapy
- curettage
- Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

**WARTS (VERRUCA VULGARIS) [HUMAN PAPILLOMAVIRUS (HPV) INFECTIONS]****Table 19. Different Manifestations of HPV Infection**

	Definition and Clinical Features	Differential Diagnosis	Distribution	HPV Type
<b>Verruca Vulgaris (Common Warts)</b>	Hyperkeratotic, elevated discrete epithelial growths with papillated surface caused by HPV Paring of surface reveals punctate, red-brown specks (thrombosed capillaries)	Molluscum contagiosum, seborrheic keratosis	Located at trauma sites: fingers, hands, knees of children and teens	At least 80 types are known
<b>Verruca Plantaris (Plantar Warts) and Verruca Palmaris (Palmar Warts)</b>	Hyperkeratotic, shiny, sharply margined growths Paring of surface reveals red-brown specks (capillaries), interruption of epidermal ridges	May need to scrape ("pare") lesions to differentiate wart from callus and corn (see sidebar, D7)	Located at pressure sites: metatarsal heads, heels, toes	Commonly HPV 1, 2, 4, 10
<b>Verruca Planae (Flat Warts)</b>	Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration Common in children	Syringoma, seborrheic keratosis, molluscum contagiosum, lichen planus	Sites: face, dorsa of hands, shins, knees	Commonly HPV 3, 10
<b>Condyloma Acuminata (Genital Warts)</b>	Skin-coloured pinhead papules to soft cauliflower like masses in clusters Often occurs in young adults, infants, children Can be asymptomatic, lasting months to years Highly contagious, transmitted sexually and non-sexually (e.g. Koebner phenomenon via scratching, shaving), and can spread without clinically apparent lesions Investigations: acetowhitening (subclinical lesions seen with 5% acetic acid x 5 min and hand lens) Complications: fairy-ring warts (satellite warts at periphery of treated area of original warts)	Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), Molluscum contagiosum	Sites: genitalia and perianal areas	Commonly HPV 6 and 11 HPV 16, 18, 31, 33 cause cervical dysplasia, SCC and invasive cancer

**Table 20. Management of Warts**

Management	Type of Wart	Notes
<b>Destructive</b>		
Cryotherapy/electrodesiccation	All	Dyschromia, pain, blisters
Surgery	Resistant	Scar, recurrence
Laser	Resistant	CO <sub>2</sub> laser
<b>Caustic Acids</b>		
Cantharidin (topical)	Small, common	Keratolytic irritation, blisters, hyperpigmentation
Mono-, di-, or tri-chloroacetic acid	Common	Irritation, blisters, scar
<b>Chemotherapeutic Agents</b>		
Podophyllotoxin*	Genital	Erythema, erosions, ulcers, pain
Bleomycin (intralesional)*	Common	Pain, nail loss/dystrophy, Raynaud's phenomenon
<b>Hypersensitivity Agents</b>		
Dinitrochlorobenzene (DNCB), diphenylcyprone	Common, plantar	Causes an allergic/hypersensitivity reaction
Candida antigen (intralesional)	Genital	Erythema, burning, erosion
Immune Response Modifiers	Genital	
5% imiquimod cream (Aldara®)*	All	
<b>Miscellaneous</b>		
No treatment	Common	65-90% resolve spontaneously over several years
Salicylic acid 40% minimum	Common, plantar	OTC, use with occlusion
Tretinoin (topical)*	Flat	Irritation
Cimetidine (oral)*	Resistant	Best in children
Canthone plus	Common, plantar	Cantharidin + podophyllin + salicylic acid
Duct tape		
± occlusion/callous scraping/paring		

\*Avoid in pregnancy

- other viruses associated with skin changes, e.g. measles, roseola, fifth disease, etc.
- see *Pediatric Exanthems*, D40

**Treatment for Skin Warts****First Line Therapies**

- Salicylic acid preparations (patches, solutions, creams, ointments)
- Cryotherapy
- Topical cantharone

**Second Line Therapies**

- Topical imiquimod
- Topical 5-Fluorouracil
- Topical tretinoin
- Podophyllotoxin

**Third Line Therapies**

- Curettage
- Cautery
- Surgery
- Laser
- Oral cimetidine (particularly children)
- Topical 5-fluorouracil
- Topical tretinoin (flat warts)
- Localized heat therapy
- Intralesional bleomycin (plantar warts)

**Treatment for Anogenital Warts****First line therapies**

- Imiquimod cream
- Podophyllotoxin (solution, cream, or gel)
- Cryotherapy

**Second line therapies**

- Trichloroacetic acid
- Topical 5-fluorouracil
- Topical tretinoin
- Electrodesiccation
- Surgical excision (with cold steel or scissors)
- CO<sub>2</sub> laser



## Yeast Infections

### CANDIDIASIS



#### Candidal Paronychia

- painful red swellings of periungual skin
- management: topical agents not as effective; oral antifungals recommended

#### Candidal Intertrigo

- macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
- peripheral "satellite" pustules
- predisposing factors: obesity, diabetes, systemic antibiotics, immunosuppression, malignancy
- starts as non-infectious maceration from heat, moisture and friction
- management: keep area dry, miconazole, ketoconazole/clotrimazole cream bid until rash clears

### PITYRIASIS (TINEA) VERSICOLOR



#### Clinical Presentation

- chronic asymptomatic superficial fungal infection with brown/white scaling macules
- affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
- sites: upper trunk most common

#### Pathophysiology

- microbe produces carboxylic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
- affinity for sebaceous glands; require fatty acids to survive

#### Etiology

- *Pityrosporum ovale* (*Malassezia furfur*)
- also associated with folliculitis and seborrheic dermatitis
- predisposing factors: summer, tropical climates, Cushing's syndrome, prolonged corticosteroid use

#### Investigations

- microscopic examination, KOH prep of scales for hyphae and spores

#### Management

- ketoconazole shampoo or cream PO daily for 7 d if more extensive
- topical terbinafine or ciclopirox olamine
- systemic fluconazole or itraconazole for 7 d



Oral Terbinafine (Lamisil®) is not effective because it is not secreted by sweat glands.

## Sexually Transmitted Infections



### SYPHILIS

#### Clinical Presentation

- characterized initially by a painless ulcer (chancre)
- following inoculation, systemic infection with secondary and tertiary stages

#### Etiology

- *Treponema pallidum*
- transmitted sexually, congenitally, or rarely by transfusion



#### Natural History of Untreated Syphilis

- Inoculation
- Primary syphilis (10-90 d after infection)
- Secondary syphilis (simultaneous to primary syphilis or up to 6 mo after healing of primary lesion)
- Latent syphilis
- Tertiary syphilis (2-20 yr)



#### Latent Syphilis

70% of untreated patients will remain in this stage for the rest of their lives and are immune to new primary infection.

Table 21. Stages of Syphilis

	Primary Syphilis	Secondary Syphilis	Tertiary Syphilis
<b>Clinical Presentation</b>	<ul style="list-style-type: none"> <li>Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate</li> <li>Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-6 wk; chancre may also develop on lips or anus</li> <li>Regional non-tender lymphadenopathy appears &lt;1 wk after onset of chancre</li> <li>DDx: chancroid (painful), HSV (multiple lesions)</li> </ul>	<ul style="list-style-type: none"> <li>Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre)</li> <li>Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia</li> <li>Lesions heal in 1-5 wk and may recur for 1 yr</li> <li>3 types of lesions:               <ol style="list-style-type: none"> <li>Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus)</li> <li>Condyloma lata: wart-like moist papules around genital/perianal region</li> <li>Mucous patches: macerated patches mainly found in oral mucosa</li> </ol> </li> </ul>	<ul style="list-style-type: none"> <li>Extremely rare</li> <li>3-7 yr after secondary</li> <li>Main skin lesion: 'Gumma' – a granulomatous non-tender nodule</li> </ul>
<b>Investigations</b>	<ul style="list-style-type: none"> <li>CANNOT be based on clinical presentation alone</li> <li>VDRL negative – repeat weekly for 1 mo</li> <li>Fluorescent treponemal antibody-syphilis (FTA-ABS) test has greater sensitivity and may detect disease earlier in course</li> <li>Dark field examination – spirochete in chancre fluid or lymph node aspirate</li> </ul>	<ul style="list-style-type: none"> <li>VDRL positive</li> <li>FTA-ABS +ve; –ve after 1 yr following appearance of chancre</li> <li>Dark field +ve in all secondary</li> </ul>	<ul style="list-style-type: none"> <li>As in primary syphilis, VDRL can be falsely negative</li> </ul>
<b>Management</b>	<ul style="list-style-type: none"> <li>Penicillin G, 2.4 million units IM, single dose</li> </ul>	<ul style="list-style-type: none"> <li>As for primary syphilis</li> </ul>	<ul style="list-style-type: none"> <li>Treatment: penicillin G, 2.4 million units IM weekly x 3 wk</li> </ul>

## GONOCOCCEMIA

### Clinical Presentation

- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

### Etiology

- Neisseria gonorrhoeae*

### Management

- notify Public Health authorities
- screen for other sexually transmitted infections (STIs)
- cefixime 400 mg PO (drug of choice) or ceftriaxone 125 mg IM

### HSV

- see *Viral Infections*, D29

### HPV

- see *Viral Infections*, D30

## Pre-Malignant Skin Conditions

### Actinic Keratosis (Solar Keratosis)

#### Clinical Presentation

- ill-defined, scaly erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

#### Pathophysiology

- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of actinic keratosis (AK) to SCC (~1/1000), but higher likelihood if AK is persistent



#### Types of Actinic Keratosis (AK)

- Erythematous: typical AK lesion
- Hypertrophic: thicker, rough papule/plaque
- Cutaneous horn: firm hyperkeratotic outgrowth
- Actinic cheilitis: confluent AKs on the lip
- Pigmented: flat, tan-brown, scaly plaque
- Spreading pigmented
- Proliferative
- Conjunctival: pinguecula, pterygium

**Epidemiology**

- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III (see sidebar, D3), rare in darker skin as melanin is protective

**Differential Diagnosis**

- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

**Investigations**

- biopsy lesions that are refractory to treatment

**Management**

- destructive: cryotherapy, electrodesiccation and curettage
- pharmacotherapy: 5-fluorouracil cream for 2-3 wk, imiquimod cream for 8-10 wk, photodynamic therapy
- excision

## Leukoplakia

**Clinical Presentation**

- a morphologic term describing homogenous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

**Pathophysiology**

- precancerous or premalignant condition
- oral form is strongly associated with tobacco use and alcohol consumption

**Epidemiology**

- 1-5% prevalence in adult population after 30 yr of age; peak at age 50
- M>F, fair-skinned
- most common oral mucosal premalignant lesion

**Differential Diagnosis**

- lichen planus, oral hairy leukoplakia

**Investigations**

- biopsy is mandatory because it is premalignant

**Management**

- low risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, follow-up
- moderate/dysplastic lesions: excision, cryotherapy

## Malignant Skin Tumours



### Non-Melanoma Skin Cancers

**BASAL CELL CARCINOMA (BCC)****Subtypes**

- noduloulcerative (typical)
  - skin-coloured papule/nodule with rolled, translucent ("pearly") telangiectatic border and depressed/eroded/ulcerated centre
- pigmented variant
  - flecks of pigment in translucent lesion with surface telangiectasia
  - may mimic malignant melanoma
- superficial variant
  - flat, tan to red-brown plaque, often with scaly, pearly border and fine telangiectasia at margin
  - least aggressive subtype
- sclerosing (morphoeaform) variant
  - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders, indurated

**Pathophysiology**

- malignant proliferation of basal keratinocytes of the epidermis
  - low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
  - usually due to UVB light exposure, therefore >80% on face
  - may also occur in previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin syndrome)

**Epidemiology**

- most common malignancy in humans
- 75% of all malignant skin tumours >40 yr, increased prevalence in the elderly
- M>F, skin phototypes I and II, chronic cumulative sun exposure

**Differential Diagnosis**

- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular malignant melanoma, SCC

**Management**

- imiquimod 5% cream (Aldara®) or cryotherapy is indicated for superficial BCCs on the trunk
- shave excision + electrodesiccation and curettage for most types of BCCs, not including morpheaform
- Mohs surgery: microscopically controlled, minimally invasive, stepwise excision for lesions on the face or in areas that are difficult to reconstruct
- radiotherapy used in advanced cases of BCC where surgical intervention is not an option
- life-long follow-up
- 95% cure rate if lesion <2 cm in diameter or if treated early

**Work-up/Investigations of Basal cell Carcinoma and other Non-melanoma Skin Cancers**

- **History:** duration, growth rate, family/personal hx of skin cancer, prior therapy to the particular lesion
- **Physical:** location, size, whether circumscribed, tethering to deep structures, full skin exam, lymph node exam
- **Biopsy:** if shallow lesion, can do shave biopsy; otherwise punch or excisional biopsy may be more appropriate

**Surgical Margins**

- **Smaller lesions:** electrodesiccation and curettage with 2-3 mm margin of normal skin
- **Deep infiltrative lesions:** surgical excision with 3-5 mm margins beyond visible and palpable tumour border, which may require skin graft or flap; or Mohs surgery, which conserves tissue and does not require margin control

**SQUAMOUS CELL CARCINOMA (SCC)****Clinical Presentation**

- indurated erythematous nodule/plaque with surface scale/crust ± ulceration
- more rapid enlargement than BCC
- sites: face, ears, scalp, forearms, dorsum of hands

**Pathophysiology**

- malignant neoplasm of keratinocytes (primarily vertical growth)
- predisposing factors include: UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar and nitrogen mustards), HPV 16, 18, immunosuppression
- may occur in previous scar (SCC more commonly than BCC)

**Epidemiology**

- second most common type of cutaneous neoplasm
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- in organ transplant recipients SCC is most common cutaneous malignancy, with increased mortality as compared to non-immunocompromised population

**Differential Diagnosis**

- benign: nummular eczema, psoriasis, irritated seborrheic keratosis
- malignant: keratoacanthoma, Bowen's disease, BCC

**Management**

- surgical excision with primary closure, skin flaps or grafting
- Mohs surgery
- lifelong follow-up (more aggressive treatment than BCC)

**Prognosis**

- good prognostic factors: early treatment, negative margins, and small size of lesion
- SCCs that arise from actinic keratosis metastasize less frequently (~1%) than other SCCs (e.g. arising de novo in old burns) (2-5% of cases)
- overall control is 75% over 5 yr, 5-10% metastasize

**OTHER FORMS OF SQUAMOUS CELL CARCINOMA (SCC)****BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)****Clinical Presentation**

- erythematous plaque with a sharply demarcated red and scaly border
- often 1-3 cm in diameter and found on the skin and mucous membranes
- evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

**Management**

- same as for BCC
- biopsy required for diagnosis
- topical 5-fluorouracil (Efudex®) or imiquimod (Aldara®) used if extensive and as a tool to identify margins of poorly defined tumours
- cryosurgery
- shave excision with electrodesiccation and curettage

**KERATOACANTHOMA****Clinical Presentation**

- rapidly growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled crater, resembling an erupting volcano
- may spontaneously regress within a year, leaving a scar
- sites: sun-exposed skin

**Pathophysiology**

- epithelial neoplasm with atypical keratinocytes in epidermis
- low grade variant of SCC

**Etiology**

- HPV, UV radiation, chemical carcinogens (tar, mineral oil)

**Epidemiology**

- >50 yr, rare <20 yr

**Differential Diagnosis**

- treat as SCC until proven otherwise
- hypertrophic solar keratosis, verruca vulgaris

**Management**

- surgical excision, treated similarly to SCC

**Malignant Melanoma (MM)****Clinical Presentation**

- malignant characteristics of a mole: see mnemonic "ABCDE"
- sites: skin, mucous membranes, eyes, CNS

**Clinical Subtypes of Malignant Melanoma**

- **lentigo maligna**
  - malignant melanoma in situ (normal and malignant melanocytes confined to the epidermis)
  - 2-6 cm, tan/brown/black uniformly flat macule or patch with irregular borders
  - lesion grows radially and produces complex colours
  - often seen in the elderly
  - 10% evolve to lentigo maligna melanoma
- **lentigo maligna melanoma** (15% of all melanomas)
  - malignant melanocytes invading into the dermis
  - associated with pre-existing solar lentigo, not pre-existing nevi
  - flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  - with time, colour changes from uniform brown to dark brown with black and blue
  - found on all skin surfaces, especially those often exposed to sun, such as the face and hands
- **superficial spreading melanoma** (60-70% of all melanomas)
  - atypical melanocytes initially spread laterally in epidermis then invade the dermis
  - irregular, indurated, enlarging plaques with red/white/blue discolouration, focal papules or nodules
  - ulcerate and bleed with growth

**Does this Patient have a Mole or Melanoma?****ABCDE checklist****Asymmetry****Border** (irregular and/or indistinct)**Colour** (varied)**Diameter** (increasing or >6 mm)**Enlargement, elevation, evolution** (i.e. change in colour, size or shape)

Sensitivity 92% (CI 82-96%)

Specificity 100% (CI 54-100%)

JAMA 1998;279:696-701

- **nodular melanoma** (30% of all melanomas)
  - atypical melanocytes that initially grow vertically with little lateral spread
  - uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
  - rapidly fatal
  - may be pink or have no colour at all, this is called an amelanotic melanoma
  - “EFG” Elevated, Firm, Growing
- **acrolentiginous melanoma** (5% of all melanomas)
  - ill-defined dark brown, blue-black macule
  - palmar, plantar, subungual skin
  - melanomas on mucous membranes have poor prognosis

### Pathophysiology

- malignant neoplasm of pigment forming cells (melanocytes and nevus cells)

### Epidemiology

- incidence 1/75 (Canada) 1/50 (US)
- risk factors: numerous moles, fair skin, red hair, positive personal/family history, large congenital nevi, familial dysplastic nevus syndrome, multiple dysplastic nevi
- most common sites: back (M), calves (F)
- worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

### Differential Diagnosis

- benign: nevi, solar lentigo, seborrheic keratosis
- malignant: pigmented BCC

### Management

- excisional biopsy preferable, otherwise incisional biopsy
- remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
- beware of lesions that regress – tumour is usually deeper than anticipated
- high dose IFN for stage II (regional), chemotherapy (cis-platinum, BCG) and high dose IFN for stage III (distant) disease
- newer chemotherapeutic, gene therapies and vaccines starting to be used in metastatic melanoma
- radiotherapy may be used as adjunctive treatment

**Table 22. American Joint Committee on Cancer Staging System Based on Breslow's Thickness of Invasion**

T1 <1.0 mm	Stage I T1a – T2a	5-yr survival 90%
T2 1.01-2.0 mm	Stage II T2b – T4b	5-yr survival 70%
T3 2.01-4.0 mm	Stage III any nodes	5-yr survival 45%
T4 >4.0 mm	Stage IV any mets	5-yr survival 10%

a = no ulceration; b = ulceration



#### Risk Factors for Melanoma

**no SPF is a SIN**

**Sun exposure**

**Pigment traits** (blue eyes, fair/red hair, pale complexion)

**Freckling**

**Skin reaction to sunlight** (increased incidence of sunburn)

**Immunosuppressive states** (e.g. renal transplantation)

**Nevi** (dysplastic nevi; increased number of benign melanocytic nevi)



#### Node Dissection for Lesions

> 1 mm thick OR < 1 mm and ulcerated OR > 1 mitoses/mm<sup>2</sup> (Stage IB or higher melanoma patients should be offered a sentinel lymph node biopsy)

- Assess sentinel node at time of wide excision

## Other Cutaneous Cancers

### CUTANEOUS T-CELL LYMPHOMA

#### Clinical Presentation

- **Mycosis fungoides** (limited superficial type)
  - characterized by: erythematous patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation)
  - common sites include: trunk, buttocks, proximal limbs
  - mildly symptomatic, usually excellent prognosis for early disease
- **Sézary syndrome** (widespread systemic type)
  - rare variant characterized by: erythroderma, lymphadenopathy, WBC >20 x 10<sup>9</sup>/L with Sézary cells
  - associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
  - often fatal

#### Pathophysiology

- clonal proliferation of skin-homing CD4 T cells

#### Epidemiology

- >50 yr old, M:F 2:1



**Differential Diagnosis**

- tinea corporis, nummular dermatitis, psoriasis, discoid lupus erythematosus, Bowen's disease

**Investigations**

- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
- blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is Sézary)
- imaging (for systemic involvement)

**Management**

- **Mycosis fungoides**
  - treatment is dependent on stage of disease
  - topical steroids and/or PUVA, narrow band (311-313 nm), UVB (NBUVB)
- **Sézary syndrome**
  - oral retinoids and IFN
  - extra-corporeal photophoresis
  - may need radiotherapy for total skin electron beam radiation
  - may maintain on UV therapy
  - other chemotherapy agents

## Alopecia (Hair Loss)



### Hair Growth

- hair grows in a cyclic pattern that is defined in 3 stages
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and DHT; this response is genetically controlled

**Hair Loss****TOP HAT**

Telogen effluvium, tinea capitis

Out of Fe, Zn

Physical: trichotillomania, "corn-row" braiding

Hormonal: hypothyroidism, androgenic

Autoimmune: SLE, alopecia areata

Toxins: heavy metals, anticoagulants, chemotherapy, vitamin A, SSRIs

## Non-Scarring (Non-Cicatricial) Alopecia

**ANDROGENETIC ALOPECIA****Clinical Presentation**

- male-pattern or female-pattern alopecia
- males: fronto-temporal areas progressing to vertex, entire scalp may be bald
- females: widening of central part, "Christmas tree" pattern

**Pathophysiology**

- action of testosterone on hair follicles

**Epidemiology**

- males: early 20s-30s
- females: 40s-50s

**Management**

- minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
- spironolactone in women (anti-androgenic effects), cyproterone acetate (Diane-35®)
- finasteride (Propecia®) (5- $\alpha$ -reductase inhibitor) 1 mg/d in men
- hair transplant

**PHYSICAL**

- trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
- traumatic (e.g. tight "corn-row" braiding of hair, wearing tight pony tails, tight tying of turbans)

**TELOGEN EFFLUVIUM****Clinical Presentation**

- uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle



**Non-scarring alopecia:** intact hair follicles on exam → biopsy not required (but may be helpful).

**Scarring alopecia:** absent hair follicles on exam → biopsy required.

**DDx of Non-scarring (non-cicatricial) Alopecia**

- **Autoimmune**
  - Alopecia areata
- **Endocrine**
  - Hypothyroidism
  - Androgens
- **Micronutrient deficiencies**
  - Iron
  - Zinc
- **Toxins**
  - Heavy metals
  - Anticoagulants
  - Chemotherapy
  - Vitamin A
- **Trauma to the hair follicle**
  - Trichotillomania
  - 'Corn-row' braiding
- **Other**
  - Syphilis
  - Severe illness
  - Childbirth

**Pathophysiology**

- precipitated by: malnutrition, Fe deficiency, thyroid dysfunction, post-partum/miscarriage, scalp diseases (seborrheic dermatitis, allergic contact dermatitis), medications (e.g. OCP), physical/mental stress
- hair loss typically occurs 2-4 mo after exposure to precipitant
- regrowth occurs within a few months but may not be complete

**ANAGEN EFFLUVIUM****Clinical Presentation**

- hair loss due to insult to hair follicle impairing its mitotic activity (growth stage)

**Pathophysiology**

- precipitated by chemotherapeutic agents (most common), other meds (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
- dose-dependent effect
- hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
- reversible effect; follicles resume normal mitotic activity few weeks after agent stopped

**ALOPECIA AREATA****Clinical Presentation**

- autoimmune disorder characterized by patches of complete hair loss often localized to scalp but can affect eyebrows, beard, eyelashes, etc.
- may be associated with dystrophic nail changes – fine stippling, pitting
- “exclamation mark” pattern (hairs fractured and have tapered shafts, i.e. looks like “!”)
- may be associated with pernicious anemia, vitiligo, thyroid disease, Addison’s disease
- spontaneous regrowth may occur within months of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress

**Management**

- generally unsatisfactory
- intralesional triamcinolone acetonide (corticosteroids) can be used for isolated patches
- UV or PUVA therapy
- immunomodulatory (diphencyprone)



**Precipitants of Telogen Effluvium**  
**“SEND”** hair follicles out of anagen and into telogen

**Stress and Scalp disease (surgery)**  
**Endocrine** (hypothyroidism, post-partum)  
**Nutritional** (iron and protein deficiency)  
**Drugs** (Acitretin, heparin, lithium, interferon,  $\beta$ -blockers, valproic acid, SSRIs)

**Alopecia Areata Subtypes**

**Alopecia totalis:** loss of all scalp hair and eyebrows

**Alopecia universalis:** loss of all body hair

**DDx of Scarring (cicatricial) Alopecia****Developmental/Hereditary Disorders**

- Aplasia cutis congenita
- Epidermal nevi
- Romberg’s syndrome
- Generalized follicular hamartoma

**Primary causes**

- Group 1: Lymphocytic
  - Discoid lupus erythematosus
  - Lichen planopilaris
  - Central centrifugal cicatricial alopecia
  - Classic Pseudopelade
- Group 2: Neutrophilic
  - Folliculitis decalvans
  - Dissecting scalp cellulitis
- Group 3: Mixed
  - Acne keloidalis nuchae

**Secondary causes**

- Infectious agents
  - Bacterial (e.g. post-cellulitis)
  - Fungal (e.g. tinea capitis)
- Neoplasms (e.g. BCC, SCC, lymphomas, and metastatic tumours)
- Physical agents
  - Mechanical trauma
  - Burns
  - Radiotherapy
  - Caustic chemicals

**Scarring (Cicatricial) Alopecia****Clinical Presentation**

- irreversible loss of hair follicles with fibrosis

**Etiology**

- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (HZV)
- inflammatory
  - lichen planus (lichen planopilaris)
  - DLE (note that SLE can cause an alopecia unrelated to discoid lupus lesions which are non-scarring)
  - morphea: “coup de sabre” with involvement of centre of scalp
  - central centrifugal cicatricial alopecia: seen in up to 40% of black women, starting at central scalp; one of most commonly diagnosed scarring alopecias, may be associated with hair care practices in this population

**Investigations**

- biopsy from active border

**Management**

- infections: treat underlying infection
- inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials

## Nails and Disorders of the Nail Apparatus



**Table 23. Nail Changes in Systemic and Dermatological Conditions**

Nail Abnormality	Definition/Etiology	Associated Disease
<b>NAIL PLATE CHANGES</b>		
Clubbing	Proximal nail plate has greater than 180 degree angle to nail fold, watch-glass nails, bulbous digits	Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.
Koilonychia	Spoon shaped nails	Iron deficiency, malnutrition, diabetes
Onycholysis	Separation of nail plate from nail bed	Psoriasis, dermatophytes, thyroid disease
Onychogryphosis	Hypertrophy of the nail plate and subungual hyperkeratosis	Poor circulation, chronic inflammation, tinea
Onychohemia	Subungual hematoma	Trauma to nail bed
Onychomycosis	Fungal infection of nail (e.g. dermatophyte, yeast, mould)	HIV, DM, peripheral arterial disease
Onychocryptosis (ingrown toenail)	Often hallux with congenital malalignment, painful inflammation, granulation tissue	Tight fitting shoes, excessive nail clipping
<b>SURFACE CHANGES</b>		
V-shaped nicking	Distal margin has v-shaped loss of the nail plate	Darier's disease (follicular dyskeratosis)
Pterygium inversus unguis	Distal nail plate does not separate from underlying nail bed	Scleroderma
Pitting	Punctate depressions that migrate distally with growth	Psoriasis (random pattern), alopecia areata (geometric, gridshaped arrangement), eczema
Transverse ridging	Transverse depressions often more in central portion of nail plate	Serious acute illness slows nail growth (when present in all nails = Beau's lines), eczema, chronic paronychia, trauma
Transverse white lines	Bands of white discolouration	Poisons, hypoalbuminemia (Muehrke's lines)
<b>COLOUR CHANGES</b>		
Yellow		Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis, tobacco use
Green		Pseudomonas
Black		Melanoma, hematoma
Brown		Nicotine use, psoriasis, poisons, longitudinal melanonychia (ethnic)
Splinter hemorrhages	Extravasation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows	Trauma, bacterial endocarditis, blood dyscrasias, psoriasis
Oil spots	Brown-yellow discolouration	Psoriasis
<b>NAIL FOLD CHANGES</b>		
Herpetic whitlow	HSV infection of distal phalanx	HSV infection
Paronychia	Local inflammation of the nail fold around the nail bed	Acute: painful infection Chronic: constant wetting (e.g. dishwashing, thumbsucking)
Nail fold telangiectasias	Cuticular hemorrhages, roughness, capillary changes	Scleroderma, SLE, dermatomyositis

## Skin Manifestations of Systemic Disease



**Table 24. Skin Manifestations of Internal Conditions**

Disease	Related Dermatoses
<b>AUTOIMMUNE DISORDERS</b>	
Behçet's disease	Painful aphthous ulcers in oral cavity ± genital mucous membranes, erythema nodosum, acneiform papules
Buerger's disease	Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital resorptions
Dermatomyositis	Periorbital and extensor violaceous erythema, heliotrope with edema, Gottron's papules (violaceous flat-topped papules with atrophy), periungual erythema, telangiectasia, calcinosis cutis
Polyarteritis nodosa	Subcutaneous nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livedo reticularis, ulceration
Rheumatic fever	Petechiae, urticaria, erythema nodosum, rheumatic nodules, evanescent rash
Scleroderma	Raynaud's, nonpitting edema, waxy/shiny/tense atrophic skin (morphea), ulcers, cutaneous calcification, periungual telangiectasia, acrosclerosis, salt-and-pepper pigmentation
Systemic lupus erythematosus	Malar erythema, discoid rash (erythematous papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy/diffuse alopecia, mucosal ulcers, photosensitivity
Crohn's Disease/Ulcerative colitis	Pyoderma gangrenosum, erythema nodosum, Sweet's syndrome



### Raynaud's Phenomenon DDx

#### COLD HAND

Cryoglobulins/Cryofibrinogens  
Obstruction/Occupational  
Lupus erythematosus, other connective tissue disease  
Diabetes mellitus/Drugs  
Hematologic problems (polycythemia, leukemia, etc)  
Arterial problems (atherosclerosis)  
Neurologic problems (vascular tone)  
Disease of unknown origin (idiopathic)

**Table 24. Skin Manifestations of Internal Conditions** (continued)

Disease	Related Dermatoses
<b>ENDOCRINE DISORDERS</b>	
Addison's disease	Generalized hyperpigmentation or limited to skin folds, buccal mucosa and scars
Cushing's syndrome	Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia
Diabetes mellitus	Infections (boils, carbuncles, <i>Candidiasis</i> , <i>S. aureus</i> , dermatophytoses, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipoidica diabetorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis
Hyperthyroidism	Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropachy, onycholysis
Hypothyroidism	Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows
<b>HIV-RELATED</b>	
Infections	Viral (HSV, HZV, HPV, CMV, molluscum contagiosum, oral hairy leukoplakia), bacterial (impetigo, acneiform folliculitis, dental caries, cellulitis, bacillary epithelioid angiomatosis, syphilis), fungal (candidiasis, histoplasmosis, cryptococcus, blastomycosis)
Inflammatory dermatoses	Seborrhea, psoriasis, pityriasis rosea, vasculitis
Malignancies	Kaposi's sarcoma, lymphoma, BCC, SCC, MM
<b>MALIGNANCY</b>	
Adenocarcinoma	
Gastrointestinal (GI)	Peutz-Jeghers: pigmented macules on lips/oral mucosa
Cervix/anus/rectum	Paget's disease: eroding scaling plaques of perineum
Carcinoma	
Breast	Paget's disease: eczematous and crusting lesions of breast
GI	Palmoplantar keratoderma: thickened skin of palms/soles
Thyroid	Sipple's syndrome: multiple mucosal neuromas
Breast/GU/lung/ovary	Dermatomyositis: heliotrope erythema of eyelids and violaceous plaques over knuckles
Lymphoma/Leukemia	
Hodgkin's	Ataxia Telangiectasia: telangiectasia on pinna, bulbar conjunctiva
Acute Leukemia	Ichthyosis: generalized scaling especially on extremities, Sweet's syndrome
	Bloom's syndrome: butterfly erythema on face, associated with short stature
Multiple Myeloma	Amyloidosis: large, smooth tongue with waxy papules on eyelids, nasolabial folds and lips, as well as facial petechiae
<b>OTHERS</b>	
Liver disease	Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry's nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice
Renal disease	Pruritus, pigmentation, half and half nails, perforating dermatosis, calciphylaxis
Pruritic urticaria papules and plaques of pregnancy	Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms and lower backs
Cryoglobulinemia	Palpable purpura in cold-exposed areas, Raynaud's, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection

**Acanthosis Nigricans**

An asymptomatic dark thickened velvety hyperpigmentation of flexural skin most commonly around the neck. Associated with diabetes, obesity and other endocrine disorders and malignancy. It is a cutaneous marker of tissue insulin resistance.

**Itchy Eruptions in Childhood****UC-SCAB**

Urticaria  
Contact dermatitis  
Scabies  
Chicken pox  
Atopic dermatitis  
Bites



## Pediatric Exanthems

**Definitions**

- exanthem: an eruption on the skin occurring as a symptom of a systemic disease typically with a fever
- enanthem: an eruption on a mucous membrane occurring in the context of an exanthem

**Table 25. Common Pediatric Exanthems**

Exanthem	Etiology	Clinical Description	Important Complications	Management
<b>Chicken Pox</b>	HHV3 Incubation 10-21 d, Communicable 1-2 d pre-rash to 5 d post-rash	Diffuse itchy vesicular pustular eruption beginning on thorax spreading to extremities New lesions every 2-3 d (multiple stage eruption: macule-papule-vesicle-crust) Enanthems	Secondary infection, necrotizing fasciitis, meningitis, encephalitis, cerebellar ataxia, pneumonitis, disseminated intravascular coagulation (DIC), hepatitis	Supportive treatment, acyclovir or valacyclovir, IV if severe; if severe, Varicella Zoster immunoglobulin (within 96 h of contact), Varicella vaccine
<b>Enteroviral</b>	Enteroviruses Most common exanthem in summer and fall	Polymorphous rash (macules, papules, vesicles, petechiae, urticaria)	None	Supportive treatment for majority Serious cases (immunosuppressed) can be treated with pleconaril
<b>Erythema Infectiosum</b>	Parvovirus B19 Incubation 4-14 d Peaks in winter and spring	Slapped cheeks (red, flushed cheeks) then 1-4 d later lacy/reticular maculo-papular rash of trunk/extremities Glove and stocking purpura	STAR complex (Sore Throat, Arthritis, Rash) Fetal infection (anemia, fetal hydrops or death) Aplastic crisis in sickle cell patients	No treatment: children often feel well NSAIDs for symptomatic arthropathy

**Table 25. Common Pediatric Exanthems** (continued)

Exanthem	Etiology	Clinical Description	Important Complications	Management
<b>Gianotti-Crosti Syndrome</b>	Epstein-Barr virus most common, hepatitis B, Coxsackie, Parvovirus Spring and early summer	Symmetric papular eruption of face, buttocks, and extremities Sparing of trunk Preceded by viral prodrome	None	Supportive treatment
<b>Hand, Foot and Mouth Disease</b>	Coxsackie A and B viruses Highly contagious virus	Vesicular eruption of palms and soles with an erosive stomatitis Enanthem: vesicles involving tongue and posterior pharynx	Pulmonary, dehydration, neurological death	Supportive treatment
<b>Kawasaki Disease</b>	Unknown etiology – infectious etiology suggested Late winter to early spring	Fever >5 d and 4/5: unilateral lymphadenopathy; puffy/red palms and soles; red, cracked lips/strawberry tongue; skin rash; non-purulent bilateral conjunctivitis	Most common cause of vasculitis and acquired heart disease in children (coronary artery aneurysm) CNS, GI tract, kidney, eyes	ASA, IVIG, baseline echo and repeat in 6 wk
<b>Measles</b>	Paramyxovirus Incubation 8-13 d Communicable 4 d pre-rash and post-rash	Morbiliform rash starts at hairline and spreads down to face/neck/trunk, desquamates (no palm or sole involvement) Prodrome: cough, coryza, conjunctivitis (3 Cs) Enanthem: Koplik spots (grey/white papules on buccal mucosa)	Otitis media, pneumonia, encephalitis, SJS, glomerular nephritis, myocarditis/pericarditis	Vitamin A, immunoglobulin, MMR vaccine
<b>Meningococemia</b>	<i>Neisseria meningitidis</i>	Purpuric and petechial rash ("stellate purpura with a central gunmetal-grey hue")	Hearing loss, intellectual disability, necrosis and loss of digits and/or limbs, septic shock, death	5-7 d course of 3rd generation cephalosporin
<b>Roseola</b>	HHV 6, HHV 7 Incubation 5-15 d	Pink macules and papules on neck/arms/trunk ± face Eruption after high fever ends Posterior cervical nodes Enanthem: Nagayama sign (red papules on soft palate)	Febrile seizures, neurological involvement Viral reactivation in immunosuppressed patients	Supportive treatment Antipyretics during the febrile period
<b>Rubella</b>	RNA virus of the Togaviridae family Incubation 14-21 d Communicable 7 d pre-rash and post-rash	1-5 d following mild prodrome (fever, headache, respiratory symptoms), a pink maculopapular rash erupts on face spreading down to neck/trunk Occipital and retroauricular nodes	STAR complex Congenital rubella (cataract, glaucoma, thrombocytopenia, hepatitis, deafness, congenital heart disease)	Supportive treatment MMR vaccine Serologic testing in rubella-exposed pregnant women
<b>Scarlet Fever</b>	GAS toxin types A, B, and C Late fall, winter, and early spring	Generalized rash, red papules, "sand-paper" texture, desquamation (palms and soles), flexural accentuation (Pastia's lines) Enanthem: strawberry tongue, petechiae on palate	Mastoiditis, otitis, sinusitis, pneumonia, meningitis, myocarditis, arthritis, hepatitis, rheumatic fever, and glomerulonephritis	10-14 d course of penicillin

## Miscellaneous Lesions



### Angioedema and Urticaria

#### Angioedema

- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
  - onset in childhood; 80% have positive family history
  - recurrent attacks; 25% die from laryngeal edema
  - triggers: minor trauma, emotional upset, temperature changes
- treatment
  - prophylaxis with danazol or stanozolol for hereditary angioedema
  - epinephrine pen to temporize until patient reaches hospital in acute attack

#### Urticaria

- also known as "hives"; see Table 26 for classification
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 h
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen



#### Wheal

- Typically erythematous flat-topped, palpable lesions varying in size with circumscribed dermal edema
- Individual lesion lasts <24 h
- Associated with mast cell release of histamine
- May be pruritic



Table 26. Classification of Urticaria

Type	Etiology
<b>Acute Urticaria</b> >2/3 of cases Attacks last <6 wk Individual lesions last <24 h	Drugs: especially ASA, NSAIDs Foods: nuts, shellfish, eggs, fruit Idiopathic (vast majority) Infection Insect stings (bees, wasps, hornets) Percutaneous absorption: cosmetics, work exposures Stress Systemic diseases: SLE, endocrinopathy, neoplasm
<b>Chronic Urticaria</b> <1/3 of cases Attacks last >6 wk Individual lesion lasts <24 h	IgE-dependent: trigger associated Idiopathic (90% of chronic urticaria patients) Aeroallergens Drugs (antibiotics, hormones, local anesthetics) Foods and additives Insect stings Parasitic infections Physical contact (animal saliva, plant resins, latex, metals, lotions, soap) Direct mast cell release Opiates, muscle relaxants, radio-contrast agents Complement-mediated Serum sickness, transfusion reactions Infections, viral/bacterial (>80% of urticaria in pediatric patients) Urticarial vasculitis Arachidonic acid metabolism ASA, NSAIDs Physical Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholinergic (hot shower, exercise), solar, pressure (shoulder strap, buttocks), aquagenic (exposure to water), adrenergic (stress), heat Other Mastocytosis, urticaria pigmentosa
<b>Urticarial Vasculitis</b> Individual lesions last >24 h Often painful, less likely pruritic, heals with bruise type lesions Requires biopsy	Idiopathic Infections Hepatitis Autoimmune diseases SLE Drug hypersensitivity cimetidine and diltiazem

**DDx for Urticaria****DAM HIVES**

Drugs and foods  
Allergic  
Malignancy  
Hereditary  
Infection  
Vasculitis  
Emotions  
Stings

**Approach to Urticaria**

- Thorough Hx and P/E
- **Acute:** if individual lesions last <24 h, but attacks last <6 wk; no immediate investigations needed; consider referral for allergy testing
- **Chronic:** if individual lesions last <24 h but attacks last >6 wk; further investigations required: CBC and differential, urinalysis, ESR, TSH  
LFTs to help identify underlying cause
- **Vasculitic:** if individual lesions last >24 h; biopsy of lesion and referral to dermatology

**Mastocytosis (Urticaria Pigmentosa)**

Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Darier's sign), due to mast cell degranulation. This occurs within minutes.



## Erythema Nodosum

**Clinical Presentation**

- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on extensor lower legs, knees, arms, (typically shins)
- associated with arthralgia, fever, malaise

**Etiology**

- 40% are idiopathic
- drugs: sulfonamides, oral contraceptives (also pregnancy), analgesics, trans retinoic acid
- infections: GAS, TB, histoplasmosis, Yersinia
- inflammation: sarcoidosis, Crohn's > UC
- malignancy: acute leukemia, Hodgkin's lymphoma

**Epidemiology**

- 15-30 yr old, F:M = 3:1
- lesions last for days and spontaneously resolve in 6 wk

**Investigations**

- chest x-ray (to rule out chest infection and sarcoidosis)
- throat culture, antistreptolysin (ASO) titre, purified protein derivative (PPD) skin test

**Management**

- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids
- treat underlying cause

**DDx of Erythema Nodosum****NODOSUMM**

No cause (idiopathic) in 40%  
Drugs (sulfonamides, OCP, etc.)  
Other infections (GAS+)  
Sarcoidosis  
Ulcerative colitis and Crohn's  
Malignancy (leukemia, Hodgkin's lymphoma)  
Many Infections



## Pruritus



### Clinical Presentation

- a sensation provoking a desire to scratch
- pruritus can present with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

### Etiology

- dermatologic – generalized
  - asteatotic dermatitis (“winter itch” due to dry skin)
  - pruritus of senescent skin (may not have dry skin, any time of year)
  - infestations: scabies, lice
  - drug eruptions: ASA, antidepressants, opiates
  - psychogenic states
- dermatologic – local
  - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin’s lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, Fe deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumours), non-Hodgkins lymphoma
  - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis



#### DDx of Pruritus

##### SCRATCHED

Scabies  
Cholestasis  
Renal  
Autoimmune  
Tumours  
Crazies (psychiatric)  
Hematology (polycythemia, lymphoma)  
Endocrine (thyroid, parathyroid, ↓ Fe)  
Drugs, Dry skin

### Investigations

- detailed history
- complete physical, including rectal and pelvic examination
- bloodwork: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture and serology for parasites

### Management

- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- topical corticosteroid and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria
- phototherapy with UVB or PUVA
- doxepin, amitriptyline
- immunosuppressive agents if severe: steroids and steroid sparing

## Wounds and Ulcers

- see [Plastic Surgery](#), PS8, PS15



## Common Medications

### Sunscreens and Preventative Therapy



#### Sunburn

- erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
- chronic UVA, UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am to 4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen



#### Key to a Wound that does Not Heal...

- Consider biopsy of any nonhealing wound to rule out cancer.



SPF = burn time with cream/burn time without cream

## Sunscreens

- under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen
- topical chemical: absorbs UV light
  - requires application at least 15-60 min prior to exposure, should be reapplied every 2 h (more often if sweating, swimming)
  - UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
  - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
- topical physical: reflects and scatters UV light
  - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride and melanin
    - ♦ all are effective against the UVA and UVB spectrum
  - less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
- some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

## Management

- sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, topical corticosteroids)
- antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin



### UV Radiation

#### UVA (320-400 nm): Aging

- Penetrates skin more effectively than UVB or UVC
- Responsible for tanning, burning, wrinkling, photoallergy and premature skin aging
- Penetrates clouds, glass and is reflected off water, snow and cement

#### UVB (290-320 nm): Burning

- Absorbed by the outer dermis
- Is mainly responsible for burning and premature skin aging
- Primarily responsible for BCC, SCC
- Does not penetrate glass and is substantially absorbed by ozone

#### UVC (200-290 nm)

- Is filtered by ozone layer



### Body Site:

#### Relative Percutaneous Absorption

Forearm	1.0
Plantar foot	0.14
Palm	0.83
Back	1.7
Scalp	3.7
Forehead	6.0
Cheeks	13.0
Scrotum	42.0

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption



### Side Effects of Topical Steroids

- Local: Atrophy  
Perioral dermatitis  
Steroid acne  
Rosacea  
Contact dermatitis  
Tachyphylaxis (tolerance)
- Systemic: Suppression of HPA axis



### Vehicles

- Ointment (water in oil): hydrate, greasy
- Cream (oil in water): hydrate, variable
- Lotion (powder in water): drying, cosmesis
- Solutions (water, alcohol, propylene glycol)
- Gel (solution that melts on contact with skin, alcohol): drying

## Topical Steroids

Table 27. Potency Ranking of Topical Steroids

Relative Potency	Relative Strength	Generic Names	Trade Names	Usage
Weak	x1	hydrocortisone 2.5% (1% available over-the-counter)	Emo Cort®	Intertriginous areas, children, face, thin skin
Moderate	x3	hydrocortisone 17-valerate – 0.2% desonide mometasone furorate	Westcort® Tridesilon® Elocom®	Arm, leg, trunk
Potent	x6	betamethasone – 0.1% 17-valerate – 0.1% amcinonide	Betnovate® Celestoderm – V® Cyclocort®	Body
Very Potent	x9	betamethasone dipropionate – 0.05% fluocinonide – 0.05% halcinonide	Diprosone® Lidex, Topsyn gel® Lyderm® Halog®	Palms and soles
Extremely Potent	x12	clobetasol propionate -0.05% (most potent) betamethasone dipropionate ointment halobetasol propionate -0.05%	Dermovate® Diprolene® Ultravate®	Palms and soles

## Dermatologic Therapies

Table 28. Common Topical Therapies

Drug Name	Dosing Schedule	Indications	Comments
Calcipotriol (Dovonex®)	0.005% cream, ointment, scalp solution, apply bid For maintenance therapy apply OD	Psoriasis	Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk > 14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)
Imiquimod (Aldara®)	5% cream applied 3x/wk Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water Max duration 16 wk	Genital warts Cutaneous warts Actinic keratosis Superficial BCC	Avoid natural/artificial sun exposure Local skin and application site reactions Erythema, ulceration, edema, flu-like symptoms Works best for warts on mucosal surfaces May induce inflammation and erosion

Table 28. Common Topical Therapies (continued)

Drug Name	Dosing Schedule	Indications	Comments
<b>Permethrin (Kwellada® P Lotion and Nix® Dermal Cream)</b>	5% cream, applied once overnight to all skin areas from neck down, repeated one week later	Scabies (Kwellada-P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)	Do not use in children <2 yr old Hypersensitivity to drug, or known sensitivity to chrysanthemums Local reactions only (resolve rapidly); including burning, pruritus Low toxicity, excellent results Consider 2nd application after 7 d
<b>Pimecrolimus (Elidel®)</b>	1.0% cream bid Use for as long as lesions persist and discontinue upon resolution of symptoms	AD (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive
<b>Tacrolimus topical (Protopic®)</b>	0.03% (children) or 0.1% (adults) ointment bid Continue for duration of disease PLUS x 1 wk after clearing	AD (mild to moderate)	Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive

Table 29. Common Oral Therapies

Drug Name	Dosing Schedule	Indications	Comments
<b>Acitretin (Soriatane®)</b>	25-50 mg PO OD; maximum 75 mg/d	Severe psoriasis Other disorders of hyperkeratinization (ichthyosis, Darier's disease)	<u>Monitoring strategies:</u> Monitor lipids, LFTs at baseline and q1-2wk until stable <u>Contraindications:</u> Women of childbearing potential unless strict contraceptive requirements are met <u>Drug interactions:</u> Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives May be combined with PUVA phototherapy (known as re-PUVA)
<b>Antivirals</b>	famcyclovir (Famvir®) 250 mg PO tid x 7-10 d (for 1st episode of genital herpes) 125 mg PO bid x 5 d (for recurrent genital herpes)  valacyclovir (Valtrex®) 1000 mg PO bid x 7-10 d (for 1st episode of genital herpes) 500 mg PO bid x 5 d (for recurrent genital herpes)	Chickenpox Herpes zoster Genital herpes Acute and prophylactic to reduce transmission in infected patients Herpes labialis	<u>Side effects:</u> Headache, nausea, diarrhea, abdominal pain Reduce dose if impaired renal function  <u>Side effects:</u> Dizziness, depression, abdominal pain Reduce dose if impaired renal function <u>Drug interactions:</u> cimetidine
<b>Cyclosporin (Neoral®)</b>	2.5-4 mg/kg/d PO div bid Max 4 mg/kg/d After 4 wk may increase by 0.5 mg/kg/d q2wks Concomitant dose of magnesium may protect the kidneys	Psoriasis May also be effective in: Lichen planus EM Recalcitrant urticaria Recalcitrant AD	<u>Monitoring strategies:</u> Blood pressure, renal function <u>Contraindications:</u> Abnormal renal function, uncontrolled hypertension, malignancy (except non-melanoma skin cancer), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug Long term effects preclude use of cyclosporin for >2 yr; discontinue earlier if possible May consider rotating therapy with other drugs to minimize adverse effects of each drug
<b>Dapsone</b>	50-100-150 mg PO OD tapering to 25-50 mg PO OD to as low as 50 mg 2x/wk	Dermatitis herpetiformis, neutrophilic dermatoses	<u>Monitoring strategies:</u> Obtain G6PD levels before initiating; in the initial two wk obtain methemoglobin levels and follow the blood counts carefully for the first few months <u>Side effects:</u> Neuropathy Hemolysis (Vitamin C and E supplementation can help prevent this) <u>Drug interactions:</u> Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major) Often a dramatic response within hours

Table 29. Common Oral Therapies (continued)

Drug Name	Dosing Schedule	Indications	Comments
<b>Isotretinoin</b> (Accutane®)	0.5-1 mg/kg/d given OD, to achieve a total dose of 120 mg/kg (20-24 wk)	Severe nodular and/or inflammatory acne Acne conglobata Recalcitrant acne Widespread comedonal acne	<u>Monitoring strategies:</u> Baseline lipid profile and LFTs before treatment, $\beta$ -HCG <u>Contraindications:</u> Teratogenic – in sexually active females, 2 forms of reliable contraception necessary Generally regarded as unsafe in lactation <u>Side effects:</u> Night blindness, decreased tolerance to contact lenses, dry mucous membranes May transiently exacerbate acne, dry skin Depression, myalgia <u>Drug interactions:</u> Do not use at the same time as tetracycline or minocycline – both may cause pseudotumour cerebri Discontinue vitamin A supplements Drug may be discontinued at 16-20 wk when nodule count has dropped by >70%. A second course may be initiated after 2 mo pm Refractory cases may require >3 courses
<b>Itraconazole</b> (Sporanox®)	100-400 mg PO OD, depending on infection treated Tinea corporis/cruris: 200 mg PO OD x 7 d Tinea pedis: 200 mg PO bid x 7 d Tinea versicolor: 200 mg PO OD x 7 d Toenails with or without fingernail involvement: 200 mg PO bid x 7 d once per month, repeated 3x Fingernail involvement only: 200 mg bid PO x 7 d once per month, repeated 2x	Onychomycosis Tinea corporis, cruris, pedis, versicolor, capitis	<u>Contraindications:</u> CHF <u>Side effects:</u> Serious hepatotoxicity <u>Drug Interactions:</u> Inhibits CYP 3A4. Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs) Give capsules with food, capsules must be swallowed whole
<b>Ivermectin</b> (Mectizan®, Stromectol®)	200-250 $\mu$ g/kg PO qweekly x 2 Take once as directed; repeat one wk later	Onchocerciasis (USA only) Not licensed for use in Canada Also effective for: Scabies	No significant serious side effects Efficacious
<b>Methotrexate</b> (Trexall®)	10-25 mg qwk, PO, IM, or IV Max: 30 mg/wk To minimize side effects, administer with folic acid supplementation: 1-5 mg OD	Psoriasis AD Lymphomatoid papulosis May also be effective in: Cutaneous sarcoidosis	<u>Monitoring strategies:</u> Baseline renal, liver, and hematological studies <u>Contraindications:</u> Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy May be combined with cyclosporine to allow lower doses of both drugs
<b>Minocycline</b> (Minocin®)	50-100 mg PO bid Taper to 50 mg PO OD as acne lessens	Acne vulgaris Rosacea	<u>Contraindications:</u> Caution if impaired renal or liver function <u>Drug interactions:</u> Do not use with isotretinoin (Accutane®) <u>Side effects:</u> Extensive; affects multiple organ systems including CNS, teeth, eyes, bones, renal, and skin (photosensitivity, and blue pigmentation) Drug-induced lupus (check p-ANCA) Alternative to tetracycline
<b>Terbinafine</b> (Lamisil®)	250 mg PO OD x 2 wk Fingernails x 6 wk Toenails x 12 wk Confirm diagnosis prior to treatment	Onychomycosis Tinea corporis, cruris, pedis, capitis	<u>Contraindications:</u> Pregnancy, chronic or active liver disease <u>Drug interactions:</u> Potent inhibitor of CYP 2D6; use with caution when also taking $\beta$ -blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics Drug concentrates rapidly in skin, hair and nails at levels associated with fungicidal activity
<b>Tetracycline</b>	250-500 mg PO bid to tid Taken 1 h before or 2 h after a meal	Acne vulgaris Rosacea Bullous pemphigoid	<u>Contraindications:</u> Severe renal or hepatic dysfunction

## References

### Textbooks

- Bolognia JL, Jorizzo JL, Rapini RP (editors). Textbook of dermatology. Vol. 1 and 2. Toronto: Mosby, 2003.
- Fitzpatrick JE and Aeling JL. Dermatology secrets. 2nd ed. Philadelphia: Hanley & Belfus, 2001.
- Goodheart H. Goodheart's photoguide to common skin disorders: diagnosis and management, 3rd ed. Philadelphia: Lippincott, Williams and Wilkins, 2008.
- Johnson RA, Suurmond D, Wolff K (editors). Colour atlas and synopsis of clinical dermatology, 5th ed. New York: McGraw Hill, 2005.
- Kraft J, Ng C, Bertucci V. University of Toronto pharmacology handbook: dermatology, (publication pending).
- Lebwohl MG, Heymann WR, Berth-Jones J, Coulson I (editors). Treatment of skin disease: comprehensive therapeutic strategies, 2nd ed. Philadelphia: Mosby, 2006.
- Paller AS, Mancini AJ. Hurwitz clinical pediatric dermatology: a textbook of skin disorders of childhood and adolescence, 3rd ed. China: Elsevier, 2006.
- Sterry W, Paus W, Burgdorf W (editors). Thieme clinical companions: dermatology, 5th ed. New York: Thieme, 2005.
- Wolff K, Johnson RA. Fitzpatrick's colour atlas and synopsis of clinical dermatology, 6th ed. New York: McGraw Hill, 2009.

### Articles

- Cribier B, et al. Erythema nodosum and associated diseases. *Int J Dermatol* 1998;637-667.
- Cummings SR, et al. Approaches to the prevention and control of skin cancer. *Cancer Metastasis Rev* 1997;16:309-327.
- DeShazo RD, et al. Allergic reactions to drugs and biologic agents. *JAMA* 1997;278:1895-1906.
- Ellis C, et al. ICCAD II Faculty. International consensus conference on atopic dermatitis II (ICCAD II): clinical update and current treatment strategies. *Br J Dermatol* 2003;148(suppl 63):3-10.
- Faergemann J, Baron R. Epidemiology, clinical presentation, and diagnosis of onychomycosis. *Br J Dermatol* 2003;149(suppl 65):1-4.
- Friedmann PS. Assessment of urticaria and angio-edema. *Clin Exper Allergy* 1999;2(suppl 3):109-112.
- Gordon ML, et al. Care of the skin at midlife: diagnosis of pigmented lesions. *Geriatrics* 1997;52:56-67.
- Krafchik, BR. Treatment of atopic dermatitis. *J Cut Med Surg* 1999;3(suppl 2):16-23.
- Mastrolorenzo A, Urbano FG, Salimbeni L, et al. Atypical molluscum contagiosum in an HIV-infected patient. *Int J Dermatol* 1998;27:378-380.
- Price VH. Treatment of hair loss. *NEJM* 1999;341:964-973.
- Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severe variants of the same disease which differs from erythema multiforme. *J Dermatol* 1997;274-276.
- Ting PT, Banankin B. Can you identify this condition? melasma. *Can Fam Phys* 2005;51:353-355.
- Walsh SRA and Shear NH. Psoriasis and the new biologic agents: interrupting a T-AP dance. *CMAJ* 2004;170:1933-1941.
- Whited JD et al. Does this patient have a mole or a melanoma? *JAMA* 1998;279:696-701.
- Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Amer Acad Dermatol* 2002;46:584-587.

Neil D. Dattani, Anandita Gokhale and Mackenzie Howatt, chapter editors

Maria Jogova and Howard Meng, associate editors

Melini Gupta, EBM editor

Dr. Mark Freedman, Dr. Fernando Teixeira and Dr. Margaret Thompson, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Ophthalmology Emergencies</b> . . . . .	<b>41</b>
<b>Initial Patient Assessment/Management.</b> . . . .	<b>2</b>	<b>Dermatologic Emergencies</b> . . . . .	<b>42</b>
Rapid Primary Survey (RPS)		Life Threatening Dermatoses	
Resuscitation		<b>Environmental Injuries</b> . . . . .	<b>43</b>
Secondary Survey		Heat Exhaustion and Heat Stroke	
Ethical Considerations		Hypothermia and Cold Injuries	
<b>Traumatology.</b> . . . .	<b>6</b>	Burns	
Considerations for Traumatic Injury		Inhalation Injury	
Head Trauma		Bites	
Mild Traumatic Brain Injury		Near Drowning	
Spine and Spinal Cord Trauma		<b>Toxicology</b> . . . . .	<b>48</b>
Chest Trauma		Alcohol Related Emergencies	
Abdominal Trauma		Approach to the Overdose Patient	
Genitourinary Tract Injuries		ABCs of Toxicology	
Orthopedic Injuries		D1 – Universal Antidotes	
Life and Limb Threatening Injuries		D2 – Draw Bloods	
Upper Extremity Injuries		D3 – Decontamination and Enhanced Elimination	
Lower Extremity Injuries		E – Expose and Examine the Patient	
Wound Management		F – Full Vitals, ECG Monitor, Foley, X-rays	
Trauma in Pregnancy		G – Give specific Antidotes and Treatments	
<b>Approach to Common ER Presentations</b> . . . .	<b>19</b>	Disposition from the Emergency Department	
Abdominal Pain		<b>Psychiatric Emergencies</b> . . . . .	<b>55</b>
Acute Pelvic Pain		Approach to Common Psychiatric Presentations	
Altered Level of Consciousness (LOC)		Acute Psychosis	
Chest Pain		Suicidal Patient	
Epistaxis		Violent Patient	
Headache		<b>Common Pediatric ER Presentations</b> . . . . .	<b>56</b>
Joint Pain		Modified Glasgow Coma Score	
Otalgia		Respiratory Distress	
Seizures		Febrile Infant and Febrile Seizures	
Shortness of Breath		Abdominal Pain	
Syncope		Common Infections	
Sexual Assault		Child Abuse and Neglect	
<b>Medical Emergencies.</b> . . . .	<b>30</b>	<b>Procedural Sedation</b> . . . . .	<b>60</b>
Anaphylaxis and Allergic Reactions		<b>Common Medications</b> . . . . .	<b>60</b>
Asthma		<b>References</b> . . . . .	<b>61</b>
Cardiac Dysrhythmias			
Chronic Obstructive Pulmonary Disease (COPD)			
Congestive Heart Failure			
DVT and Pulmonary Embolism			
Diabetic Emergencies			
Electrolyte Disturbances			
Hypertensive Emergencies			
Stroke			
<b>Gynecology/Urology Emergencies.</b> . . . .	<b>39</b>		
Vaginal Bleed			
Pregnant Patient in the ER			
Nephrolithiasis (Renal Colic)			



## Acronyms

AAA	abdominal aortic aneurysm	ETT	endotracheal tube	NS	normal saline
ABG	arterial blood gas	FAST	focused abdominal sonogram for trauma	OD	overdose
ACS	acute coronary syndrome	FFP	fresh frozen plasma	PE	pulmonary embolism
AVN	avascular necrosis	GCS	Glasgow coma scale	PID	pelvic inflammatory disease
AVPU	alert, voice, pain, unresponsive	IBD	inflammatory bowel disease	PNS	parasympathetic nervous system
AXR	abdominal x-ray	IBS	irritable bowel syndrome	pRBC	packed red blood cells
Bi-PAP	bilevel positive airway pressure	ICP	intracranial pressure	ROM	range of motion
CPAP	continuous positive airway pressure	ICS	intercostal space	RSI	rapid sequence induction
CPP	cerebral perfusion pressure	JVP	jugular venous pressure	rt-PA	recombinant tissue plasminogen activator
CSF	cerebrospinal fluid	LP	lumbar puncture	SNS	sympathetic nervous system
CVA	costovertebral angle	LOC	level of consciousness	SOB	shortness of breath
CXR	chest x-ray	LVH	left ventricular hypertrophy	TBI	traumatic brain injury
D&C	dilatation and curettage	MAP	mean arterial pressure	U/A	urinalysis
DM	diabetes mellitus	MDI	metered dose inhaler	U/S	ultrasound
DRE	digital rectal exam	MVC	motor vehicle collision	UTox	urine toxicology screen
DVT	deep venous thrombosis	NG	nasogastric	VBG	venous blood gas
ED	emergency department				

## Initial Patient Assessment/Management



### 1. Rapid Primary Survey (RPS)

- Airway maintenance with cervical spine (C-spine) control
  - Breathing and ventilation
  - Circulation (pulses, hemorrhage control)
  - Disability (neurological status)
  - Exposure (complete) and Environment (temperature control)
  - continually reassessed during secondary survey
- IMPORTANT:** always watch for signs of shock while doing primary survey (see Table 1)

#### A. AIRWAY

- first priority is to secure airway
- assume a cervical injury in every trauma patient and immobilize with collar
- assess ability to breathe and speak
- can change rapidly, therefore reassess frequently

#### Airway Management

- permit adequate oxygenation and ventilation

#### 1. Basic Airway Management (Temporizing Measures)

- protect the C-spine
- head-tilt (if C-spine injury not suspected) or jaw thrust to open the airway
- sweep and suction to clear mouth of foreign material

#### 2. Temporizing Measures

- nasopharyngeal airway (if gag reflex present, i.e. conscious)
- oropharyngeal airway (if gag reflex absent, i.e. unconscious)
- “rescue” airway devices [e.g. laryngeal mask airway (LMA); Combitube®]
- transtracheal jet ventilation through cricothyroid membrane (last resort)

#### 3. Definitive Airway Management

- ETT intubation with in-line stabilization of C-spine (Figure 1)
  - orotracheal ± RSI preferred
  - nasotracheal – may be better tolerated in conscious patient
    - ♦ relatively contraindicated with basal skull fracture
  - does not provide 100% protection against aspiration
- surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
  - cricothyroidotomy

#### Contraindications to Intubation

- supraglottic/glottic pathology that would preclude successful intubation



#### Approach to the Critically Ill Patient

1. Rapid Primary Survey (RPS)
2. Resuscitation (often concurrent with RPS)
3. Detailed Secondary Survey
4. Definitive Care



Noisy breathing is obstructed breathing until proven otherwise.



#### Signs of Airway Obstruction

- Agitation, confusion, “universal choking sign”
- Respiratory distress
- Failure to speak, dysphonia
- Cyanosis



#### Medications that can be Delivered via ETT

**NAVEL**  
 Naloxone (Narcan®)  
 Atropine  
 Ventolin® (salbutamol)  
 Epinephrine  
 Lidocaine



#### Requirements for Clearing the C-Spine

- No midline tenderness
- No focal neurological deficits
- No distracting factors such as intoxication, altered LOC or distracting injuries

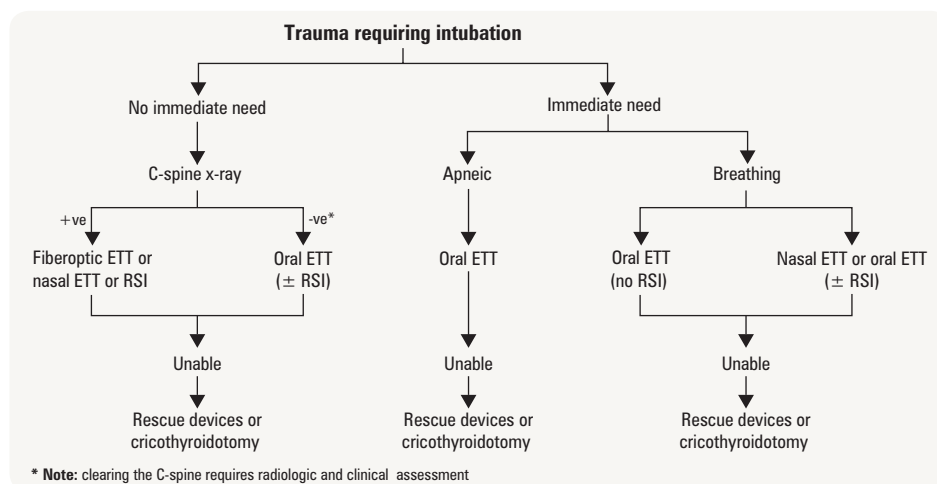


Figure 1. Approach to endotracheal intubation in an injured patient

## B. BREATHING

### • Look

- mental status (anxiety, agitation, decreased LOC), colour, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring

### • Listen

- auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping

### • Feel

- tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

## Breathing Assessment

- objective measures of respiratory function: rate, oximetry, arterial blood gas (ABG), A-a gradient

## Management of Breathing

- nasal prongs → simple face mask → non-rebreather mask → CPAP/BiPAP (in order of increasing  $F_iO_2$ )
- Venturi mask: used to precisely control  $O_2$  delivery
- Bag-Valve mask and CPAP to supplement inadequate ventilation

## C. CIRCULATION

### Definition of Shock

- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities) (see Table 2)

Table 1. Major Types of Shock

Hypovolemic	Cardiogenic	Distributive (vasodilation)	Obstructive
Hemorrhage (external and internal)	Myocardial ischemia	Septic	Cardiac tamponade
Severe burns	Dysrhythmias	Anaphylactic	Tension pneumothorax
High output fistulas	Congestive heart failure	Neurogenic (spinal cord injury)	Pulmonary embolism
Dehydration (diarrhea, DKA)	Cardiomyopathies		Aortic stenosis
	Cardiac valve problems		Constrictive pericarditis

### Clinical Evaluation

- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities and reduced central venous pressure (CVP)
- late: hypotension and altered mental status, reduced urine output

Table 2. Estimation of Degree of Hemorrhagic Shock

Class	I	II	III	IV
Blood loss	<750 cc	750-1500 cc	1500-2000 cc	>2000 cc
% of blood volume	<15%	15-30%	30-40%	>40%
Pulse	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Respiratory rate	20	30	35	>45
Capillary refill	Normal	Decreased	Decreased	Decreased
Urinary output	30 cc/h	20 cc/h	10 cc/h	None
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood



### Indications for Intubation

- Unable to protect airway (e.g. Glasgow Coma Scale (GCS) <8; airway trauma)
- Inadequate oxygenation with spontaneous respiration ( $O_2$  saturation <90% with 100%  $O_2$  or rising  $pCO_2$ )
- Profound shock
- Anticipatory: in trauma, overdose, CHF, asthma, COPD and smoke inhalation injury
- Anticipated transfer of critically ill patients



### Rescue Techniques in Intubation

- Bougie (used like a guidewire)
- Glidescope®
- Lighted stylet (use light through skin to determine if ETT in correct place)
- Fiberoptic intubation – indirect visualization using fiberoptic cable



Shock in a trauma patient is hemorrhagic until proven otherwise.



### Signs of Fluid Depletion

- Increased heart rate
- Postural changes in vital signs
- Decreased urine output
- Hypotensive
- Decreased skin turgor
- Sunken eyes
- Decreased capillary refill



### Causes of Shock

#### SHOCKED

Septic, spinal/neurogenic, Hemorrhagic

Obstructive (e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism)

Cardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)

anaphylactic

Endocrine (e.g. Addison's, myxedema, coma)

Drugs



### Estimated Systolic Blood Pressure Based on Position of Most Distal Palpable Pulse

	sBP (mmHg)
Radial	>80
Femoral	>70
Carotid	>60

## Management of Hemorrhagic Shock

- ABCs
- diagnose and manage underlying cause
- if bleeding externally, apply direct pressure and elevate extremities if possible
  - do not remove impaled objects as they tamponade hemorrhage
  - tourniquet as a last resort
- resuscitation
  - infuse 1-2 L of crystalloid with large bore IVs (warmed if possible)
  - if inadequate response, consider active internal bleeding (e.g. chest, abdomen, pelvis, femurs), will likely require surgical intervention
  - if severely hypotensive on arrival or if shock persists, consider pRBC transfusion
  - transfuse crossmatched (ideally) or type-specific blood if available
  - if unavailable, transfuse O-negative in children/women of child bearing age or O-positive in all others
  - with significant blood loss, early transfusion of platelets and FFP may improve outcomes

## D. DISABILITY

- assess level of consciousness by AVPU method or GCS (Table 3)

## Glasgow Coma Scale (GCS)

- for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- most useful if repeated and used for monitoring of trend
- change in GCS with time is more relevant than the absolute number
- less meaningful for metabolic coma
- patient with deteriorating GCS needs immediate attention
- prognosis based on best post-resuscitation GCS
- reported as a 3 part score: Eyes + Verbal + Motor = Total (see Table 3)
- if patient intubated, GCS score reported out of 10 + T (T= tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

Eyes Open		Best Verbal Response		Best Motor Response	
Spontaneously	4	Answers questions appropriately	5	Obeys commands	6
To voice	3	Confused, disoriented	4	Localizes to pain	5
To pain	2	Inappropriate words	3	Withdraws from pain	4
No response	1	Incomprehensible sounds	2	Decorticate (flexion)	3
		No verbal response	1	Decerebrate (extension)	2
				No response	1

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury

See Table 30 for modified GCS for infants and children

## E. EXPOSURE/ENVIRONMENT

- undress patient completely and assess entire body for injury; logroll to examine back
- digital rectal exam
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)



### Fluid Resuscitation

- Give bolus until HR decreases, urine output increases, and patient stabilizes
- Maintenance: 4:2:1 rule
- 0-10 kg: 4 cc/kg/h
- 10-20 kg: 2 cc/kg/h
- Remaining weight: 1 cc/kg/h
- Replace ongoing losses and deficits (assume 10% of body weight)



### 3:1 Rule

Since only 30% of infused isotonic crystalloids remains in intravascular space, you must give 3x estimated blood loss.



### Initial Management of Any Patient in Shock

- ABCs
- IV fluids
- Oxygen
- Monitor (HR, BP, urine, mentation, O<sub>2</sub> saturation)
- Control hemorrhage



### Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

NEJM 2008;358:877-887

**Study:** Multicentre, randomized, double-blind trial

**Patients:** 778 patients with septic shock

**Intervention:** Low-dose vasopressin (0.01 to 0.03 U per minute) or norepinephrine (5 to 15 ug per minute) in addition to open-label vasopressors and a minimum of 5 ug of norepinephrine.

**Outcome:** Mortality rate 28 d after start of infusions.

**Results:** No significant difference between the vasopressin and the norepinephrine groups at 28 d or 90 d. However, in patients with less severe septic shock, mortality rate was lower in the vasopressin group.



### Contraindications to Foley insertion

- Blood at urethral meatus
- Scrotal hematoma
- High-riding prostate on DRE

## 2. Resuscitation

- done concurrently with primary survey
- attend to ABCs (see Table 4)
- manage life-threatening problems as they are identified
- vital signs q5-15 min
- ECG, BP and O<sub>2</sub> monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type

Table 4. 2010 AHA CPR Guidelines

Step/Action	Adult: >8 years	Child: 1-8 years	Infant: <1 year
Airway	Head tilt-chin lift		
Breaths	2 breaths at 1 second/breath – stop once see chest rise		
Foreign-body airway obstruction	Abdominal thrust		Back slaps and chest thrusts
<b>Compressions</b>			
Compression landmarks	In the centre of the chest, between nipples		Just below nipple line
Compression method: push hard and fast and allow for complete recoil	2 hands: heel of 1 hand with second hand on top	2 hands: heel of 1 hand with second on top, or 1 hand: heel of 1 hand only	2 fingers, or thumbs
Compression depth	At least 2 inches	About 1/3 to 1/2 the depth of the chest	
Compression rate	100/min		
Compression-ventilation ratio	30 compressions to 2 ventilations		
Compression-only CPR	Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only		
<b>Defibrillation</b>	Immediate defibrillation for all rescuers responding to a sudden witnessed collapse Compressions (5 cycles/2 min) before AED is considered if unwitnessed arrest Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available		

**NG Tube Contraindications**

- Significant mid-face trauma
- Basal skull fracture



See [Anesthesia](#), A28 for 2012 ACLS Guidelines.

## 3. Secondary Survey

- done after rapid primary survey problems have been addressed
- identifies major injuries or areas of concern
- full physical exam and x-rays (C-spine, chest, pelvis – required in blunt trauma, consider T-spine and L-spine)

### HISTORY

- “SAMPLE”: Signs and symptoms, Allergies, Medications, Past medical history, Last meal, Events related to injury

### PHYSICAL EXAMINATION

#### Head and Neck

- pupils
  - assess equality, size, symmetry, reactivity to light
    - ♦ inequality/sluggish suggests local eye problem or lateralizing CNS lesion
    - ♦ relative afferent pupillary defect (swinging light test) – optic nerve damage
    - ♦ extraocular movements and nystagmus
    - ♦ fundoscopy (papilledema, hemorrhages)
  - reactive pupils + decreased LOC → metabolic or structural cause
  - non-reactive pupils + decreased LOC → structural cause (especially if asymmetric)
- palpation of facial bones, scalp

#### Chest

- inspect for midline trachea, flail segment:  $\geq 2$  rib fractures in  $\geq 2$  places; if present look for associated hemothorax, pneumothorax, and contusions
- auscultate lung fields
- palpate for subcutaneous emphysema
- CXR

#### Abdomen

- assess for peritonitis, abdominal distention, and evidence of intra-abdominal bleeding
- FAST or CT (if stable)
- rectal exam for GI bleed, high riding prostate and anal tone (best to do during the log roll)
- bimanual exam in females as appropriate

#### Musculoskeletal (MSK)

- examine all extremities for swelling, deformity, contusion, tenderness, ROM
- check for pulses and sensation in all injured limbs
- log roll and palpate thoracic and lumbar spines
- palpate iliac crests and pubic symphysis, pelvic stability (lateral, AP, vertical)
- pelvic x-ray


**Unilateral, Dilated, Non-reactive Pupil, think:**

- Focal mass lesion
- Epidural hematoma
- Subdural hematoma



Non-contrast head CT is the best imaging modality for intracranial injury.


**Signs of Increased Intracranial Pressure (ICP)**

- Deteriorating LOC (hallmark)
- Deteriorating respiratory pattern
- Cushing reflex (high BP, low heart rate, irregular respirations)
- Lateralizing CNS signs (e.g. cranial nerve palsies, hemiparesis)
- Seizures
- Papilledema (occurs late)
- Nausea/vomiting and headache

## Neurological

- GCS
- full cranial nerve exam
- alterations of rate and rhythm of breathing are signs of structural or metabolic abnormalities
  - progressive deterioration of breathing pattern implies a failing CNS
- assess spinal cord integrity
  - conscious patient: assess distal sensation and motor
  - unconscious patient: response to painful or noxious stimulus applied to extremities

## Ethical Considerations

### Consent to Treatment: Adults

- see [Ethical, Legal and Organizational Aspects of Medicine](#), ELOAM5
- Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury AND obtaining consent is either: a) not possible OR b) would increase risk to the patient
  - assumes that most people would want to be saved in an emergency
- any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
- exceptions to the Emergency Rule: treatment cannot be initiated if
  - a competent patient has previously refused the same or similar treatment and there is no evidence to suggest the patient's wishes have changed
  - an advanced directive is available – e.g. do not resuscitate (DNR) order
  - NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
- if in doubt, initiate treatment
  - care can be withdrawn if necessary at a later time or if wishes are clarified by family

### Consent to Treatment: Children

- treat immediately if patient is at imminent risk
- parents/guardians have the right to make treatment decisions
- if parents refuse treatment that is life-saving or will potentially alter the child's quality of life, Children's Aid Society (CAS) must be contacted – consent of CAS is needed to treat

### Other Issues of Consent

- need consent for HIV testing, as well as for administration of blood products
- however, if delay in substitute consent for blood transfusions puts patient at risk, transfusions can be given

### Duty to Report

- law may vary depending on province and/or state
- examples: gunshot wounds, potential drunken drivers, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others



#### Jehovah's Witnesses

- Capable adults have the right to refuse medical treatment
- May refuse whole blood, pRBCs, platelets and plasma even if life-saving
- Should be questioned directly about the use of albumin, immunoglobulins, hemophilic preparations
- Do not allow autologous transfusion unless there is uninterrupted extra corporeal circulation
- Usually ask for the highest possible quality of care without the use of the above interventions (e.g. crystalloids for volume expansion, attempts at bloodless surgery)
- Patient will generally sign hospital forms releasing medical staff from liability
- Most legal cases involve children of Jehovah's Witnesses; if life-saving treatment is refused contact CAS

## Traumatology

- epidemiology
  - leading cause of death in patients <45 yr
  - 4th highest cause of death in North America
  - causes more deaths in children/adolescents than all diseases combined
- trimodal distribution of death
  - minutes: lethal injuries, death usually at the scene
  - early: death within 4-6 h – “golden hour” (decreased mortality with trauma care)
  - days-weeks: death from multiple organ dysfunction, sepsis, etc.
- injuries fall into two categories
  - blunt (most common): motor vehicle collision (MVC), pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  - penetrating (increasing in incidence): gunshot wound, stabbing, impalement

## Considerations for Traumatic Injury

- important to know the mechanism of injury in order to anticipate traumatic injuries
- always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- always inquire about head injury, loss of consciousness, amnesia, vomiting, headache and seizure activity

**Table 5. Mechanisms and Considerations of Traumatic Injuries**

Mechanism of Injury	Special Considerations	Associated Injuries
<b>Motor Vehicle Collision</b>	Vehicle(s) involved: weight, size, speed, damage Location of patient in vehicle Use and type of seatbelt Ejection of patient from vehicle Entrapment of patient under vehicle Airbag deployment Helmet use in motorcycle collision	Head-on collision: head/face, thoracic (aortic), lower extremity, Lateral/T-bone collision: head, cervical spine, thoracic, abdominal, pelvic and lower extremity. Rear-end collision: hyper-extension of cervical spine (whiplash injury) Rollover
<b>Pedestrian-Automobile Impact</b>	High morbidity and mortality Vehicle speed is an important factor Site of impact on car	Children at increased risk of being run over (multisystem injuries) Adults tend to be struck in lower legs (lower extremity injuries), impacted against car (truncal injuries) and thrown to ground (head injuries)
<b>Falls</b>	1 storey = 12 feet = 3.6 m Distance of fall: 50% mortality at 4 stories and 95% mortality at 7 stories Landing position (vertical vs. horizontal)	Vertical: lower extremity, pelvic and spine fractures. Head injuries Horizontal: facial, upper extremity and rib fractures. Abdominal, thoracic and head injuries
<b>Gunshot Wounds (GSW)</b>	Type of gun Type of ammunition Range of shot Characterize route of entry, even or odd number of wounds and site of exit wound (if any) $KE = 1/2 mv^2$	Injuries dependent on location of GSW and underlying structures Hand gun: low/medium velocity, extent of injury may be limited to small area Hunting rifle: high velocity, widespread injury Shotgun: widespread tissue destruction at close range, massive tissue destruction, deposition of wadding into wound
<b>Stab Wounds (SW)</b>	Route/direction of entry Length of blade Type of penetration (stab, slash, impalement) If blade in-situ, DO NOT REMOVE – may be tamponading vessel (to be removed in OR)	Injuries dependent on location of SW and underlying structures



### High Risk Injuries

- MVC at high speed, resulting in ejection from vehicle
- Motorcycle collisions
- Vehicle vs. pedestrian crashes
- Fall from height > 12 ft (3.6 m)



### Vehicle vs. Pedestrian Crash

In adults look for triad of injuries (Waddle's triad):

- Tibia-fibula or femur fracture
- Truncal injury
- Craniofacial injury



**Cardiac box:** sternal notch, nipples and xiphoid process; injuries inside this area should increase suspicion of cardiac injury.



Always completely expose and count the number of wounds.

## Head Trauma

- see [Neurosurgery](#), NS30
- 60% of trauma admissions have head injuries
- 60% of MVC-related deaths are due to head injury

### Specific Injuries

- **fractures**
  - Dx: non-contrast head CT and physical exam
- A. skull fractures
  - vault fractures
    - ♦ linear, non-depressed
      - most common
      - typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
    - ♦ depressed
      - open (associated overlying scalp laceration and torn dura, skull fracture disrupting paranasal sinuses or middle ear) vs. closed
  - basal skull
    - ♦ typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
    - ♦ clinical diagnosis superior as poorly visualized on CT (Battle's sign, raccoon eyes, CSF rhinorrhea/otorrhea, hemotympanum)
- B. facial fractures (see [Plastic Surgery](#), PL28)
  - neuronal injury
  - beware of open fracture or sinus fractures (risk of infection)
  - unstable or displaced fractures (need semi-urgent plastics referral)
  - severe facial fractures may pose risk to airway from profuse bleeding



Falls and MVCs are the leading cause of head trauma.



### Signs of Basal Skull Fracture

- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF Rhinorrhea/Otorrhea





- **scalp laceration**

- can be a source of significant bleeding
- achieve hemostasis, inspect and palpate for skull bone defects ± CT head (rule-out skull fracture)

- **neurological injury**

- A. diffuse

- mild traumatic brain injury = concussion
  - ♦ transient alteration in mental status that may involve loss of consciousness
    - hallmarks of concussion: confusion and amnesia, which may occur immediately after the trauma or minutes later
    - loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15 and post-traumatic amnesia must be less than 24 h
- diffuse axonal injury
  - ♦ mild: coma 6-24 h, possibly lasting deficit
  - ♦ moderate: coma >24 h, little or no signs of brainstem dysfunction
  - ♦ severe: coma >24 h, frequent signs of brainstem dysfunction

- B. focal injuries

- contusions
- intracranial hemorrhage (epidural, subdural, intracerebral)

**Warning Signs of Severe Head Injury**

- GCS <8
  - Deteriorating GCS
  - Unequal pupils
  - Lateralizing signs
- N.B.** Altered LOC is a hallmark of brain injury

**ASSESSMENT OF BRAIN INJURY****History**

- pre-hospital status
- mechanism of injury

**Physical Examination**

- assume C-spine injury until ruled out
- vital signs
  - shock (not likely due to isolated brain injury, except in infants)
  - Cushing's response to increasing ICP (bradycardia, hypertension, irregular respirations)
- severity of injury determined by
  1. LOC
    - ♦ GCS ≤8 intubate, any change in score of 3 or more = serious injury
    - ♦ mild TBI = 13-15, moderate = 9-12, severe = 3-8
  2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
  3. lateralizing signs (motor/sensory)
    - ♦ may become more subtle with increasing severity of injury
- reassess frequently

**Investigations**

- labs: CBC, electrolytes, PT/PTT or INR/PTT, glucose, toxicology screen
- CT scan (non-contrast) to exclude intracranial mass lesions
- C-spine imaging, often with CT head and neck to exclude intracranial mass lesions

**Management**

- goal in ED: reduce secondary injury by avoiding hypoxia, ischemia, decreased CPP, seizure
- general
  - ABCs
  - ensure oxygen delivery to brain through intubation and prevent hypercarbia
  - maintain BP (sBP >90)
  - treat other injuries
- early neurosurgical consultation for acute and subsequent patient management
  - medical management
    - ♦ seizure treatment/prophylaxis
      - benzodiazepines, phenytoin, phenobarbital
      - steroids are of no proven value
    - ♦ treat suspected raised ICP → consider if head injury with signs of increased ICP:
      - raise head of stretcher 20° if patient hemodynamically stable
      - intubate and hyperventilate (100% O<sub>2</sub>) to a pCO<sub>2</sub> of 30-35 mmHg
      - mannitol 1g/kg infused as rapidly as possible (contraindicated in shock and renal failure/anuria)
      - consider paralyzing medications if agitated/high airway pressures
      - maintenance of CPP is critical (CPP=MAP-ICP)

**Disposition**

- neurosurgical ICU admission for severe head injuries (HI)
- in hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
- for minor head injury not requiring admission, provide 24 h HI protocol to competent caregiver, follow-up with neurology as even seemingly minor HI may cause lasting deficits

**Canadian CT Head Rule**

*Lancet 2001;357:1391-1396*

**CT Head is only required for patients with minor head injuries with any one of the following:**

**High risk** (for neurological intervention)

- GCS score <15 at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid otorrhea/rhinorrhea, Battle's sign)
- Vomiting ≥2 episodes
- Age ≥65 yr

**Medium risk** (for brain injury on CT)

- Amnesia before impact >30 min (i.e. cannot recall events just before impact)
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs)

**Minor head injury** is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.

**NB:** Canadian CT head rule does not apply for non-trauma cases, for GCS <13, age <16, for patients on Coumadin® and/or having a bleeding disorder, or having an obvious open skull fracture

**Treatment of Increased ICP**

- Elevate head of bed
- Mannitol
- Hyperventilate
- Paralyzing/sedating agents

See also [Neurosurgery](#), NS6

## Mild Traumatic Brain Injury

### Epidemiology

- traumatic brain injury results in 1.7 million deaths, hospitalizations and ED visits each year (US)
- 75% are estimated to be mild TBI; remainder are moderate or severe (see [Neurosurgery](#), NS31)
- highest rates in children 0-4 yr, adolescents 15-19 yr and elderly >65 yr

### Clinical Features

- somatic: headache, sleep disturbance, nausea, vomiting, blurred vision
- cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
- emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils

### Etiology

- falls, motor vehicle and traffic accidents, struck by an object, assault, sports

### Investigations

- neuro exam
- concussion recognition tool (see [thinkfirst.ca](#))
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

### Treatment

- close observation and follow-up; patients at risk of intracranial complications [give appropriate discharge instructions to patient and family] watch for changes to clinical features above, and if change, return to ER
- hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
- early rehabilitation to maximize outcomes
- pharmacological management of pain, depression, headache
- follow Return to Play guidelines: Cantu, Colorado Medical Society, American Academy of Neurology, 2008 Consensus Statement on Concussion in Sports – no data on superiority

### Prognosis

- most recover with minimal treatment
  - athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema or permanent impairment



Extent of retrograde amnesia correlates with severity of injury.



**Collar everyone with at least one of the following criteria**

- Midline tenderness
- Neurological symptoms or signs
- Significant distracting injuries
- Head injury
- Intoxication
- Dangerous mechanism
- History of altered LOC



Patients with penetrating trauma (especially gunshot and knife wounds) can also have spinal cord injury.



Of the investigations, the lateral C-spine x-ray is the single most important film. 95% of radiologically visible abnormalities are found on this film.



Cauda Equina Syndrome can occur with any spinal cord injury below T10 vertebrae. Look for incontinence, anterior thigh pain, quadriceps weakness, abnormal sacral sensation, decreased rectal tone and variable reflexes.



**The Canadian C-spine Rule versus the NEXUS Low-risk Criteria in Patients with Trauma**  
*NEJM* 2003;349:2510-2518

**Purpose:** To compare the clinical performance of the Canadian C-Spine Rule (CCR) and the National Emergency X-Radiography Utilization Study (NEXUS) Low-Risk Criteria (NLC).

**Study:** Trauma patients (n=8283) in stable condition were prospectively evaluated by both the CCR and NLC by 394 physicians before radiography. 2% of these patients had a C-spine injury.

**Results:** Compared to the NLC, the CCR was more sensitive (99.4 vs. 90.7%) and more specific (45.1 vs. 36.8%) after exclusion of indeterminate cases. The number of missed patients would be 1 for the CCR and 16 for the NLC. The range of motion was not evaluated in some CCR cases likely because physicians were not comfortable with the procedure and this may slightly lower the sensitivity or specificity of the CCR in practice.

**Summary:** The CCR is superior to the NLC in alert and stable patients with trauma. The use of the CCR can result in lower radiography rates.

## Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (Figure 2)
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (SCIWORA = spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

### History

- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

### Physical Exam

- ABCs
- abdo: ecchymosis, tenderness
- neuro: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; logroll, then palpate T-spine and L-spine spine; assess rectal tone
  - when palpating assess for tenderness, muscle spasm, bony deformities, step-off and spinous process mal-alignment
- extremities: check cap refill, suspect thoracolumbar injury with calcaneal fractures

### Investigations

- labs: CBC, electrolytes, creatinine, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - full C-spine x-ray series for trauma (AP, lateral, odontoid)
- thoracolumbar x-rays
  - AP and lateral views
  - indications:
    - patients with C-spine injury
    - unconscious patients (with appropriate mechanism of injury)
    - patients with neurological symptoms or findings

- ♦ patients with deformities that are palpable when patient logroll
- ♦ patients with back pain
- ♦ patients with bilateral calcaneal fractures (due to fall from height)
  - concurrent burst fractures of the lumbar or thoracic spine in 10% (T11-L2)
- consider CT (for subtle bony injuries), MRI (for soft tissue injuries) if appropriate

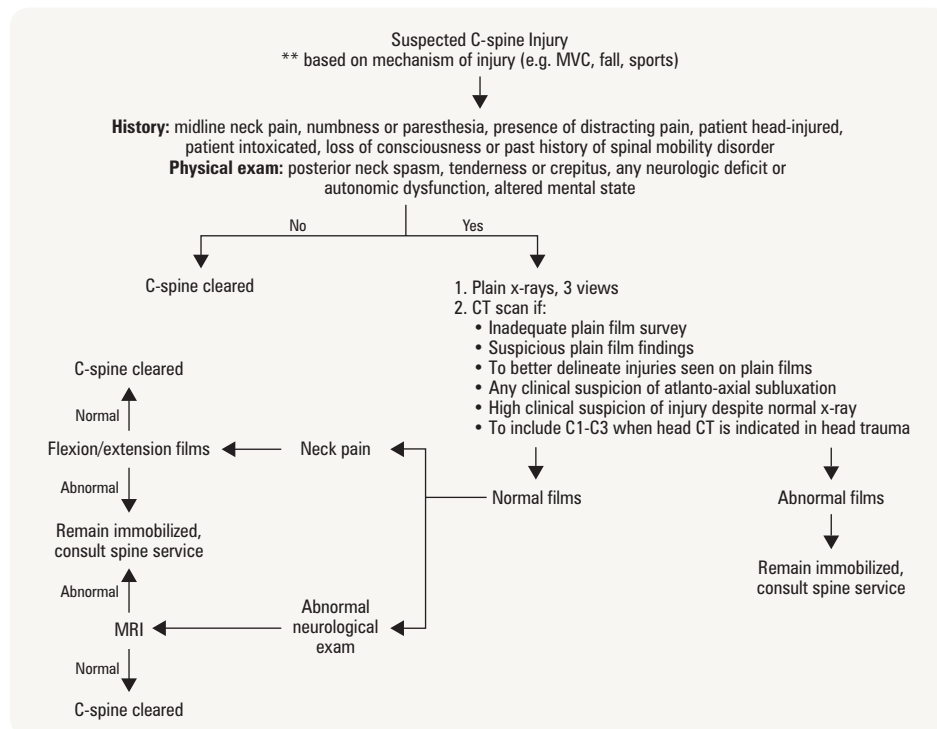


Figure 2. Approach to clearing the C-spine

### Can Clear C-spine if:

- no posterior midline cervical tenderness
- no evidence of intoxication
- oriented to person, place, time and event
- no focal neurological deficits
- no painful distracting injuries (e.g. long bone fracture)

### Management of Cord Injury

- immobilize
- evaluate ABCs
- treat shock (maintain sBP >100 mmHg)
- insert NG and Foley catheter
- high dose steroids: methylprednisolone 30 mg/kg bolus, then 5.4 mg/kg/h drip, start within 6-8 h of injury (controversial and recently has less support)
- complete imaging of spine and consult spine service if available
- continually reassess high cord injuries as edema can travel up cord
- if cervical cord lesion, watch for respiratory insufficiency
  - low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact)
  - high cervical cord injury (above C4) may require intubation and ventilation
- beware of hypotension (neurogenic shock)
- treatment: warm blanket, Trendelenburg position (occasionally), volume infusion, consider vasopressors

### Approach to C-Spine X-Rays

- 3-view C-spine series is the screening modality of choice
  1. lateral C1-T1 ± swimmer's view (Figure 3, see Table 6 for interpretation)
    - ♦ lateral view is best, identifies 90-95% of injuries
  2. odontoid view (open mouth or oblique submental view) (see Figure 4)
    - ♦ examine the dens for fractures
    - if unable to rule out fracture, repeat view or consider CT or plain film tomography
    - ♦ examine lateral aspects of C1 and spacing relative to C2
  3. AP view
    - ♦ alignment of spinous processes in the midline
    - ♦ spacing of spinous processes should be equal
    - ♦ check vertebral bodies and facet dislocations



### The Canadian C-Spine Rule

JAMA 2001; 286:1841-1848

For Alert (Glasgow Coma Scale Score = 15) and Stable Trauma Patients where Cervical Spine (C-spine) injury is a concern

1. Any high-risk factor that mandates radiography?  
 Age ≥65 yr  
 or  
 Dangerous mechanism\*  
 or  
 Paresthesias in extremities

No

2. Any one low-risk factor that allows safe assessment of range of motion?  
 Simple rear-end MVC†  
 or  
 Sitting position in ED  
 or  
 Ambulatory at any time  
 or  
 Delayed onset of neck pain‡  
 or  
 Absence of midline C-spine tenderness

Yes

3. Able to actively rotate neck?  
 >45° left and right

Unable

Able

No radiography

\*Dangerous Mechanism:

- Fall from ≥1 meter/5 stairs
- Axial load to head e.g. diving
- MVC high speed (>100 km/h), rollover, ejection
- Motorized recreational vehicles
- Bicycle collision

†Simple rear-end MVC excludes:

- Pushed into oncoming traffic
- Hit by bus/large truck
- Rollover
- Hit by high-speed vehicle

‡Delayed: Not immediate onset of neck pain

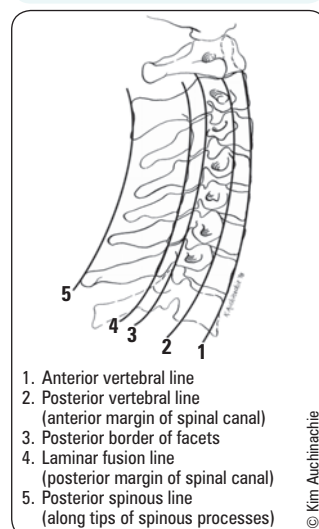


Figure 3. Lines of contour on a lateral C-spine x-ray



Prevertebral soft tissue swelling is only 49% sensitive for injury.

## Supine Oblique Views

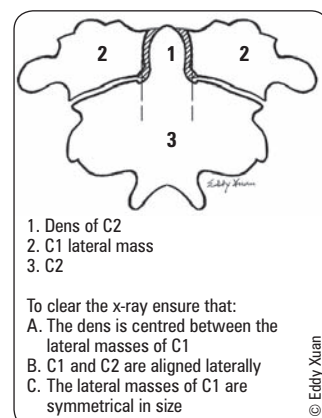
- rarely used
- better visualization of posterior element fractures (lamina, pedicle, facet joint)
- good to assess patency of neural foramina
- can be used to visualize the C7-T1 junction

**Table 6. Interpretation of Lateral View: The ABCS**

<b>A Adequacy and Alignment</b>	<ul style="list-style-type: none"> <li>• Must see C1 to C7-T1 junction; if not, downward traction of shoulders, swimmer's view, bilateral supine obliques, or CT scan needed</li> <li>• Lines of contour – in children &lt;8 yr of age: can see physiologic subluxation of C2 on C3, and C3 on C4, but the spino-laminal line is maintained</li> <li>• Fanning of spinous processes – suggests posterior ligamentous disruption</li> <li>• Widening of facet joints</li> <li>• Check atlanto-occipital joint:</li> <li>• Line extending inferiorly from clivus should transect odontoid</li> <li>• Atlanto-axial articulation – widening of predental space (normal: &lt;3 mm in adults, &lt;5 mm in children) indicates injury of C1 or C2</li> </ul>
<b>B Bones</b>	<ul style="list-style-type: none"> <li>• Height, width and shape of each vertebral body</li> <li>• Pedicles, facets, and laminae should appear as one – doubling suggests rotation</li> </ul>
<b>C Cartilage</b>	<ul style="list-style-type: none"> <li>• Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression</li> </ul>
<b>S Soft Tissues</b>	<ul style="list-style-type: none"> <li>• Widening of retropharyngeal (normal: &lt;7 mm at C1-4, may be wide in children &lt;2 yr on expiration) or retrotracheal spaces (normal: &lt;22 mm at C6-T1, &lt;14 mm in children &lt;5 yr)</li> </ul>

## Sequelae of C-spine Fractures

- see [Neurosurgery](#), NS 32
- acute phase of SCI
  - spinal shock: absence of all voluntary and reflex activity below level of injury
    - ♦ decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
  - neurogenic shock: loss of vasomotor tone, SNS tone
    - ♦ watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
    - ♦ occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
    - ♦ provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
- chronic phase of SCI
  - autonomic dysreflexia: in patients with an SCI at level T6 or above
    - ♦ signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
    - ♦ common triggers
      - GU causes: bladder distention, urinary tract infection, and kidney stones
      - GI causes: fecal impaction or bowel distension
    - ♦ treatment: monitoring and controlling BP, prior to addressing causative issue



**Figure 4. C-spine x-ray; odontoid view**



In contrast to neurogenic shock, hypovolemic shock has hypotension and tachycardia.



Autonomic dysreflexia – a life threatening elevation of BP with SCI at or above T6.



20% of C-spine fractures are accompanied by other spinal fractures, so ensure thoracic and lumbar spine x-rays are normal before proceeding to OR.



Trauma to the chest accounts for 50% of trauma deaths.



80% of all chest injuries can be managed non-surgically with simple measures such as intubation, chest tubes, and pain control.



**3-way Seal for Open Pneumothorax (i.e. sucking chest wound)**  
Allows air to escape during the expiratory phase (so that you don't get a tension pneumothorax) but seals itself to allow adequate breaths during the inspiratory phase.



**Pulsus Paradoxus:** a drop in BP of >10 mmHg with inspiration. Recall that BP normally drops with inspiration, but what's "paradoxical" about this is that it drops more than it should.

## Chest Trauma

- two types: those found and managed in 1° survey and those found and managed in 2° survey (see Tables 7 and 8)

**Table 7. Life-Threatening Chest Injuries Found in 1° Survey**

	Physical Exam	Investigations	Management
<b>Airway Obstruction</b>	<ul style="list-style-type: none"> <li>• Anxiety, stridor, hoarseness, altered mental status</li> <li>• Apnea, cyanosis</li> </ul>	<ul style="list-style-type: none"> <li>• Do not wait for ABG to intubate</li> </ul>	<ul style="list-style-type: none"> <li>• Definitive airway management</li> <li>• Intubate early</li> <li>• Remove foreign body if visible with laryngoscope prior to intubation</li> </ul>
<b>Tension Pneumothorax</b>	<ul style="list-style-type: none"> <li>• Respiratory distress, tachycardia, distended neck veins, cyanosis, asymmetry of chest wall motion</li> <li>• Tracheal deviation away from pneumothorax</li> <li>• Percussion hyperresonance</li> <li>• Unilateral absence of breath sounds</li> </ul>	<ul style="list-style-type: none"> <li>• Non-radiographic diagnosis</li> </ul>	<ul style="list-style-type: none"> <li>• Needle thoracostomy – large bore needle, 2nd intercostal space (ICS) mid clavicular line, followed by chest tube in 5th ICS, anterior axillary line</li> </ul>

Table 7. Life-Threatening Chest Injuries Found in 1<sup>o</sup> Survey (continued)

	Physical Exam	Investigations	Management
<b>Open Pneumothorax</b> • Air entering chest from wound rather than trachea	• Gunshot or other wound (hole >2/3 tracheal diameter) ± exit wound • Unequal breath sounds	• ABG: decreased pO <sub>2</sub>	• Air-tight dressing sealed on 3 sides • Chest tube • Surgery
<b>Massive Hemothorax</b> • >1500 cc blood loss in chest cavity	• Pallor, flat neck veins, shock • Unilateral dullness • Absent breath sounds, hypotension	• Usually only able to do supine CXR – entire lung appears radioopaque as blood spreads out over posterior thoracic cavity	• Restore blood volume • Chest tube • Thoracotomy if: • >1500 cc total blood loss • ≥200 cc/h continued drainage
<b>Flail Chest</b> • Free-floating segment of chest wall due to >2 rib fractures, each at 2 sites • Underlying lung contusion (cause of morbidity and mortality)	• Paradoxical movement of flail segment • Palpable crepitus of ribs • Decreased air entry on affected side	• ABG: decreased pO <sub>2</sub> , increased pCO <sub>2</sub> • CXR: rib fractures, lung contusion	• O <sub>2</sub> + fluid therapy + pain control • Judicious fluid therapy in absence of systemic hypotension • Positive pressure ventilation • ± intubation and ventilation
<b>Cardiac Tamponade</b> • Clinical diagnosis • Pericardial fluid accumulation impairing ventricular function	• Penetrating wound (usually) • Beck's triad: hypotension, distended neck veins, muffled heart sounds • Tachycardia, tachypnea • Pulsus paradoxus • Kussmaul's sign (increased JVP with inspiration)	• Echocardiogram • Bedside ultrasound (FAST)	• IV fluids • Pericardiocentesis • Open thoracotomy

Table 8. Potentially Life-Threatening Chest Injuries Found in 2<sup>o</sup> Survey

	Physical Exam	Investigations	Management
<b>Pulmonary Contusion</b>	• Blunt trauma to chest • Interstitial edema impairs compliance and gas exchange	• CXR: areas of opacification of lung within 6 h of trauma	• Maintain adequate ventilation • Monitor with ABG, pulse oximeter and ECG • Chest physiotherapy • Positive pressure ventilation if severe
<b>Ruptured Diaphragm</b>	• Blunt trauma to chest or abdomen (e.g. high lap belt in MVC)	• CXR: abnormality of diaphragm/lower lung fields/ NG tube placement • CT scan and endoscopy – sometimes helpful for diagnosis	• Laparotomy for diaphragm repair and because of associated intra-abdominal injuries
<b>Esophageal Injury</b>	• Usually penetrating trauma (pain out of proportion to degree of injury)	• CXR: mediastinal air (not always) • Esophagram (Gastrografin®) • Flexible esophagoscopy	• Early repair (within 24 h) improves outcome but all require repair
<b>Aortic Tear</b> • 90% tear at subclavian (near ligamentum arteriosum), most die at scene • Salvageable if diagnosis made rapidly	• Sudden high speed deceleration (e.g. MVC, fall, airplane crash), complaints of chest pain, dyspnea, hoarseness (frequently absent) • Decreased femoral pulses, differential arm BP (arch tear)	• CXR, CT scan, transesophageal echo (TEE), aortography (gold standard) • See sidebar for CXR features	• Thoracotomy (may treat other severe injuries first)
<b>Blunt Myocardial Injury (rare)</b>	• Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose) • Physical examination: overlying injury, e.g. fractures, chest wall contusion	• ECG: dysrhythmias, ST changes • Patients with a normal ECG and normal hemodynamics never get dysrhythmias	• O <sub>2</sub> • Antidysrhythmic agents • Analgesia

## Other Potentially Life-Threatening Injuries Related to the Chest

### Penetrating Neck Trauma

- includes all penetrating trauma to the three zones of the neck (Figure 5)
- management: injuries deep to platysma require further evaluation by angiography, contrast CT or surgery
- do not explore penetrating neck wounds except in the OR

### Airway Injuries

- always maintain a high index of suspicion



### DDx of Life Threatening Chest Injuries

#### HOT and FAT CHEST

Hemothorax\*  
Open pneumothorax  
Tension pneumothorax\*

Flail chest  
Airway obstruction  
Tamponade\*

Contusion: pulmonary, myocardial  
Hernia: traumatic, diaphragmatic  
ESophageal perforation  
Tracheobronchial disruption/  
Traumatic injury/Thoracic Aorta Rupture\*

\*Rapidly Life Threatening



Ruptured diaphragm is more often diagnosed on the left side, as liver conceals right side defect.



### Aortic Tear: ABC WHITE

x-ray features of Aortic tear  
depressed left mainstem Bronchus  
pleural Cap  
Wide mediastinum (most consistent)  
Hemothorax  
Indistinct aortic knuckle  
Tracheal deviation to right side  
Esophagus (NG tube) deviated to right

(Note: present in 85% of cases, but cannot rule out)



### If Penetrating Neck Trauma Present, DON'T:

- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaed object

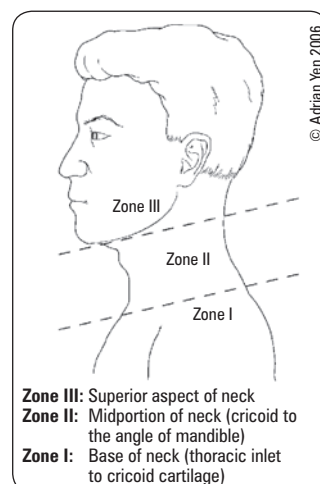


Figure 5. Zones of the neck in trauma



- larynx
  - history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma
  - triad: hoarseness, subcutaneous emphysema, palpable fracture crepitus
  - other symptoms: hemoptysis, dyspnea, dysphonia
  - investigations: CXR, CT scan, arteriography (if penetrating)
  - management
    - ♦ airway: manage early because of edema
    - ♦ C-spine may also be injured, consider mechanism of injury
    - ♦ surgical: tracheotomy vs. repair
- trachea/bronchus
  - frequently missed
  - history: deceleration, penetration, increased intra-thoracic pressure; complaints of dyspnea, hemoptysis
  - examination: subcutaneous air, Hamman's sign (crunching sound synchronous with heart beat)
  - CXR: mediastinal air, persistent pneumothorax or persistent air leak after chest tube inserted for pneumothorax
  - management: surgical repair if >1/3 circumference

## Abdominal Trauma

- two mechanisms
  - blunt: usually causes solid organ injury (spleen = most common, liver = 2<sup>nd</sup>)
  - penetrating: usually causes hollow organ injury or liver injury (most common)

### BLUNT TRAUMA

- results in two types of hemorrhage: intra-abdominal and retroperitoneal
- adopt high clinical suspicion of bleeding in multi-system trauma

### History

- mechanism of injury, SAMPLE history

### Physical Exam

- often unreliable in multi-system trauma, wide spectrum of presentations
  - slow blood loss not immediately apparent
  - other injuries may mask symptoms
  - serial examinations are required
- abdomen
  - inspect: contusions, abrasions, seatbelt sign, distention
  - auscultate: bruits, bowel sounds
  - palpate: tenderness, rebound tenderness, rigidity, guarding
  - DRE: rectal tone, blood, bone fragments, prostate location
  - placement of NG, Foley catheter should be considered part of the abdominal exam
- other systems to assess: cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

### Investigations

- labs: CBC, electrolytes, coagulation, cross and type, glucose, creatinine, CK, lipase, amylase, liver enzymes, ABG, blood EtOH,  $\beta$ -hCG, U/A, toxicology screen
- imaging: see Table 9

**Table 9. Imaging in Abdominal Trauma**

Imaging	Strengths	Limitations
<b>X-Ray</b>	Chest (looking for free air under diaphragm, diaphragmatic hernia, air-fluid levels), pelvis, cervical, thoracic, lumbar spines	Soft tissue not well visualized
<b>CT scan</b>	Most specific test	Radiation exposure 20x more than x-ray Cannot use if hemodynamic instability
<b>Diagnostic Peritoneal Lavage (DPL) (rarely used)</b>	Most sensitive test Tests for intra-peritoneal bleed	Cannot test for retroperitoneal bleed or diaphragmatic rupture Cannot distinguish lethal from trivial bleed Results can take up to 1 h
<b>Ultrasound: FAST</b>	Identifies presence/absence of free fluid in peritoneal cavity RAPID exam: less than 5 min Can also examine pericardium and pleural cavities	NOT used to identify specific organ injuries If patient has ascites, FAST will be falsely positive



#### Seatbelt Injuries may Cause:

- Retroperitoneal duodenal trauma
- Intraperitoneal bowel transection
- Mesenteric injury
- L-spine injury



#### Indications for Foley and NG Tube in Abdominal Trauma

Foley catheter: unconscious or patient with multiple injuries who cannot void spontaneously.  
Contraindications: blood at the meatus, an ecchymotic scrotum, or a "high-riding" prostate on DRE (retrograde cystourethrogram is indicated to rule out a urethral tear or ruptured bladder).

NG tube: used to decompress the stomach and proximal small bowel.  
Contraindications: facial fractures or basal skull fractures suspected.



#### Criteria for Positive Lavage

- > 10 cc gross blood
- Bile, bacteria, foreign material
- RBC count > 100,000  $\times 10^6/L$
- WBC > 500  $\times 10^6/L$ , amylase > 175 IU



- imaging must be done if
  - equivocal abdominal examination, suspected intra-abdominal injury or distracting injuries
  - multiple trauma patient resulting in unreliable physical exam (altered sensorium, secondary to drugs, alcohol, head trauma, or distracting injury; spinal cord injury resulting in abdominal anesthesia)
  - unexplained shock/hypotension
  - multiple trauma patients who must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
  - fractures of lower ribs, pelvis, spine
  - positive FAST

### Management

- general: ABCs, fluid resuscitation and stabilization
- surgical: watchful waiting vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion of injury: admit and observe for 24 h

### PENETRATING TRAUMA

- high risk of gastrointestinal perforation and sepsis
- history: size of blade, calibre/distance from gun, route of entry
- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  - thoracoabdominal region (may cause pneumothorax)
  - back or flanks (muscles too thick)

### Management

- general: ABCs, fluid resuscitation and stabilization
- gunshot wounds → always require laparotomy



#### Laparotomy is mandatory if penetrating trauma and:

- Shock
- Peritonitis
- Evisceration
- Free air in abdomen
- Blood in NG tube, Foley catheter, or on rectal exam



#### "Rule of Thirds" for stab wounds:

- 1/3 do not penetrate peritoneal cavity
- 1/3 penetrate but are harmless
- 1/3 cause injury requiring surgery

## Genitourinary Tract Injuries

- see [Urology](#), U32

### Etiology

- blunt trauma: often associated with pelvic fractures
  - upper tract
    - ♦ renal
      - contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
      - parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
    - ♦ ureter: rare, at uretero-pelvic junction
  - lower tract
    - ♦ bladder
      - extraperitoneal rupture of bladder from pelvic fracture fragments
      - intraperitoneal rupture of bladder from trauma and full bladder
    - ♦ urethra
      - posterior urethral injuries: MVCs, falls, pelvic fractures
      - anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
  - external genitalia
- penetrating trauma
  - damage to: kidney, bladder, ureter (rare), external genitalia
- acceleration/deceleration injury
  - renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
- iatrogenic
  - ureter and urethra (from instrumentation)

### History

- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension



Gross hematuria suggests bladder injury.

## Physical Examination

- abdominal pain, flank pain, costovertebral angle (CVA) tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen
- urethral injury: perineal ecchymosis, scrotal hematoma, blood at penile meatus, high riding prostate, pelvic fractures

## Investigations

- urethra: retrograde urethrography
- bladder: urinalysis, CT scan, urethrogram, ± retrograde cystoscopy, ± cystogram (distended bladder + post-void)
- ureter: retrograde ureterogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram (IVP)

## Management

- urology consult
- renal
  - minor injuries: conservative management
    - ♦ bedrest, hydration, analgesia, antibiotics
  - major injuries: admit
    - ♦ conservative management with frequent reassessments, serial urinalysis, ± re-imaging
    - ♦ surgical repair (exploration, nephrectomy): e.g. hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis
- ureter
  - uretero-uretostomy
- bladder
  - extraperitoneal
    - ♦ minor rupture: Foley drainage x 10-14 d
    - ♦ major rupture: surgical repair
  - intraperitoneal
    - ♦ drain abdomen and surgical repair
- urethra
  - anterior: conservative, if cannot void → Foley or suprapubic cystostomy and antibiotics
  - posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair



In the case of gross hematuria, the GU system is investigated from distal to proximal (i.e. urethrogram, cystogram, etc.).

## Orthopedic Injuries

- see [Orthopedics](#) (Shoulder OR10, Knee, OR29 Wrist OR19, Ankle OR35)

## Goals of ED Treatment

- diagnose potentially life/limb threatening injuries
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

## History

- use SAMPLE
- mechanism of injury may be very important

## Physical Examination

- look (inspection): “SEADS” Swelling, Erythema, Atrophy, Deformity, Skin changes (e.g. bruises)
- feel (palpation): all joints/bones – local tenderness, swelling, warmth, crepitus, joint effusions, subtle deformity
- move: joints affected plus those above and below injury – active ROM preferred to passive
- neurovascular status: distal to injury (before and after reduction)



### Description of Fractures

#### SOLARTAT

Site  
Open vs. closed  
Length  
Articular  
Rotation  
Translation  
Alignment/Angulation  
Type (e.g. Salter-Harris, etc.)

## LIFE AND LIMB THREATENING INJURIES

**Table 10. Life and Limb Threatening Orthopedic Injuries**

Life Threatening Injuries (usually blood loss)	Limb Threatening Injuries (usually interruption of blood supply)
Major pelvic fractures	Fracture/dislocation of ankle (talar AVN)
Traumatic amputations	Crush injuries
Massive long bone injuries (beware of fat emboli)	Compartment syndrome
Vascular injury proximal to knee/elbow	Open fractures
	Dislocations of knee/hip
	Fractures above knee/elbow

### Open Fractures

- communication between fracture site and external surface of skin – increased risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- must secure definitive surgical care within 6-8 h

### Vascular Injuries

- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

### Compartment Syndrome

- increased interstitial pressure in an anatomical “compartment” (forearm, calf) with little room for expansion, resulting in decreased perfusion and potential muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - look for “the 6 Ps” (see side bar)
- requires prompt decompression: remove constrictive casts, dressings; fasciotomy may be needed emergently

## UPPER EXTREMITY INJURIES

- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
    - reduce (traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with ortho
    - with forceful injury, look for fracture
- Colles' fracture (Figure 6)
  - distal radius fracture with dorsal displacement from Fall On an Outstretched Hand (FOOSH)
  - AP film: shortening, radial deviation, radial displacement
  - lateral film: dorsal displacement, volar angulation
  - reduce, immobilize with splint, out-patient follow-up with ortho or immediate orthopedic referral if complicated fracture
  - if involvement of articular surface, emergent orthopedic referral
- scaphoid fracture (see Figure 7 for review of carpal bones)
  - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
  - negative x-ray: thumb spica splint, re-x-ray in 1 wk ± bone scan
  - positive x-ray: thumb spica splint x 6-8 wk, re-x-ray in 2 wk
  - risk of AVN of scaphoid if not immobilized
  - outpatient ortho follow-up

## LOWER EXTREMITY INJURIES

- ankle and foot fractures
  - see Ottawa Ankle and Foot Rules (Figure 8)
- knee injuries
  - see Ottawa Knee Rules (Figure 9)



### Reasons for Emergent Orthopedic Consultation

- Compartment syndrome
- Irreducible dislocation
- Circulatory compromise
- Open fracture
- Injury requiring surgical repair



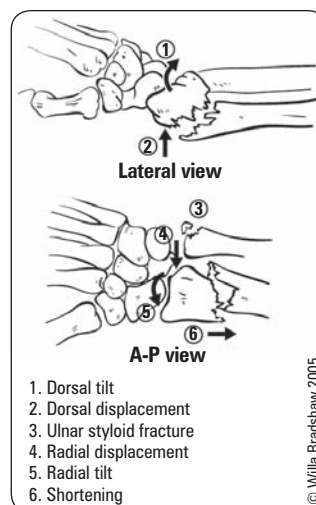
### When Dealing with an Open Fracture, Remember “STAND”

**S**plint  
**T**etanus prophylaxis  
**A**ntibiotic  
**N**eurovascular status (before and after)  
**D**ressings (to cover wound)

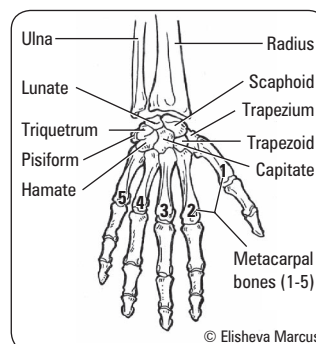


Vascular injury/compartment syndrome is suggested by “The 6 Ps”:

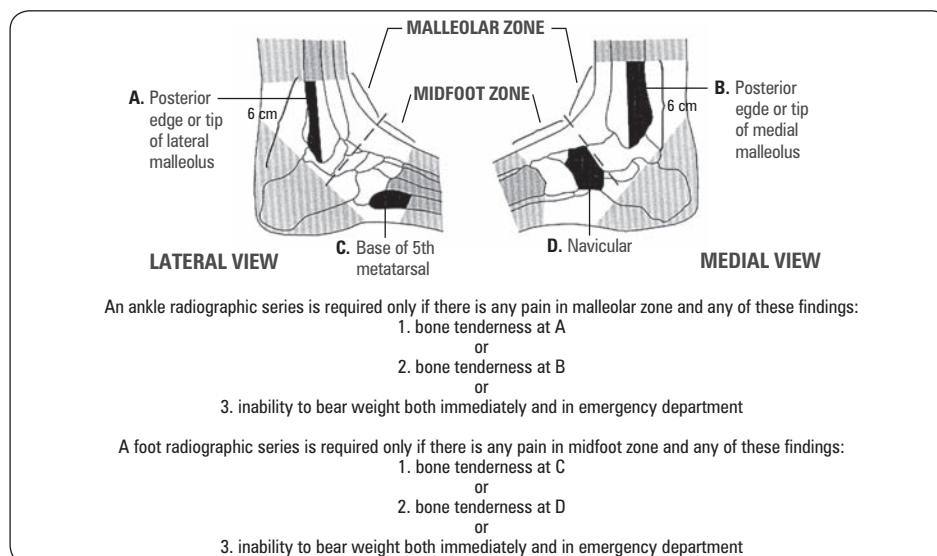
**P**ulse discrepancies  
**P**allor  
**P**aresthesia/hypoesthesia  
**P**aralysis  
**P**ain (especially when refractory to usual analgesics)  
**P**olar (cold)



**Figure 6. Colles' fracture**



**Figure 7. Carpal bones**



**Figure 8. Ottawa Ankle and Foot Rules**

Adapted from Stiell et. al. JAMA 1994;271:827-832

- avulsion of the base of 5th metatarsal
  - occurs with inversion injury
  - supportive tensor or below knee walking cast for 3 wk
- calcaneal fracture
  - associated with fall from height
  - associated injuries may involve ankles, knees, hips, pelvis, lumbar spine

**A knee x-ray examination is required only for acute injury patients with one or more of:**

- Age 55 yrs or older
- Tenderness at head of fibula
- Isolated tenderness of patella
- Inability to flex to 90°
- Inability to bear weight both immediately and in the emergency department (four steps)

**Figure 9. Ottawa Knee Rules**

Adapted from: Stiell et. al. JAMA 1997; 278:2075-2079

## Wound Management

### Goals of ED Treatment

- identify injuries and stop any active bleeding – direct pressure
- manage pain
- wound examination and exploration (history and physical)
- cleansing ± antibiotic and tetanus prophylaxis
- closure and dressing

### Tetanus Prophylaxis

- both tetanus toxoid (Td) and immunoglobulin (TIG) are safe in pregnancy

**Table 11. Guidelines for Tetanus Prophylaxis for Wounds**

Immunization History	Non Tetanus Prone Wounds		Tetanus Prone Wounds <sup>1</sup>	
	Td <sup>2</sup>	TIG <sup>3</sup>	Td	TIG
Uncertain or <3 doses	Yes	No	Yes	Yes
3 or more, none for >10 yr	Yes	No	Yes	No
3 or more, 5 to 10 yr ago	No	No	Yes	No
3 or more, <4 yr ago	No	No	No	No

<sup>1</sup> wounds >6 h old, >1 cm deep, puncture wounds, avulsions, wounds resulting from missiles, crush wounds, burns, frostbite, wounds contaminated with dirt, feces, soil, or saliva

<sup>2</sup> 0.5 mL IM tetanus and diphtheria toxoids (Td), adsorbed

<sup>3</sup> tetanus immune globulin (TIG), 250 units deep IM

Source: MMWR 2001;50:418-427; MMWR 1991;40:1-52



### Accuracy of Ottawa Ankle Rules to Exclude Fractures of the Ankle and Mid-Foot: Systematic Review

BMJ 2003;326:417

This systematic review and meta-analysis of 27 studies including 15,581 patients evaluated the sensitivity and specificity of the Ottawa Ankle Rules for excluding fractures of the ankle and mid-foot.

**Results:** The pooled likelihood ratio of a negative result (obtaining a false negative) among those with a fracture was determined to be 0.08 for both the ankle and mid-foot.

**Reviewers' Conclusions:** The Ottawa Ankle Rules provide an accurate instrument for excluding fractures of the ankle and mid-foot with a sensitivity of almost 100% and a specificity of 26%. The use of this instrument can reduce the number of unnecessary radiographs.



### Acute Treatment of Contusions

#### RICE

Rest  
Ice  
Compression  
Elevation



### Suture Use and Duration

Suture to	Close with nylon or other nonabsorbable suture	Approx. duration (days)
Face	6-0	5
Not Joint	4-0	7
Joint	3-0	10
Scalp	4-0	7
Mucous Membrane	absorbable (vicryl)	N/A

N.B. Patients on steroid therapy may need sutures for longer periods of time

## Bruises

- non-palpable = ecchymosis
- palpable collection (not swelling) = hematoma following blunt trauma
- assess for coagulopathy (e.g. liver disease), anticoagulant use

## Abrasions

- partial to full thickness break in skin
- management
  - clean thoroughly, ± local anesthetic, with brush to prevent foreign body impregnation
  - antiseptic ointment (Polysporin® or Vaseline®) for 7 d for facial and complex abrasions
  - tetanus prophylaxis (Table 11)

## Lacerations

- see also [Plastic Surgery](#), PL8
- consider every structure deep to a laceration injured until proven otherwise
- in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury
- physical exam
  - think about underlying anatomy
  - examine tendon function actively against resistance and neurovascular status distally
  - clean and explore under local anesthetic; look for partial tendon injuries
  - x-ray or ultrasound wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radiopaque), or if suspect intra-articular involvement
- management
  - disinfect skin/use sterile techniques
  - irrigate copiously with normal saline
  - analgesia ± anesthesia
  - maximum dose of lidocaine:
    - ♦ 7 mg/kg with epinephrine
    - ♦ 5 mg/kg without epinephrine
- in children, topical anesthetics such as LET (lidocaine, epinephrine and tetracaine) and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
- secure hemostasis
- evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
- ± prophylactic antibiotics (consider for animal/human bites, intraoral lesion or puncture wounds to the foot)
- suture unless: delayed presentation (>6-8 h), puncture wound, mammalian bite, crush injury or retained foreign body
  - take into account patient and wound factors when considering suturing
- advise patient when to have sutures removed
- cellulitis and necrotising fasciitis, see [Plastic Surgery](#), PL14



### Alternatives to Sutures

- Tissue glue
- Steristrips®
- Staples



Where **NOT** to use local anesthetic with epinephrine:

**Ears, Nose, Fingers, Toes and Penis**



### High Risk Factors for Infection

- Puncture wounds
- Crush injuries
- Wounds greater than 12 h old
- Hand or foot wounds, wounds near joints
- Immunocompromised patient
- Patient age greater than 50 yr
- Prosthetic joints or valves (risk of endocarditis)



Early wound irrigation and debridement are the most important factors in decreasing infection.



Since cellulitis can cause edema, remember to elevate the leg to decrease discomfort. Treat with antibiotics, analgesics and close follow-up.

## Trauma in Pregnancy

- priorities: airway, breathing, circulation

### Hemodynamic Considerations (changes that mimic shock)

- near term, inferior vena caval compression in the supine position can decrease cardiac output by 30-40% (see *Maternal Physiology*, [Obstetrics](#), OB3)
  - use left lateral decubitus (LLD) positioning or hip bolster to alleviate compression and increase blood return if BP is low
- BP drops 5-15 mmHg systolic in 2nd trimester, increases to normal by term
- HR increases 15-20 beats per minute by 3rd trimester

### Blood Considerations

- physiologic macrocytic anemia of pregnancy (Hb 100-120 g/L)
- WBC increases to a high of 20,000
- blood volume increase in pregnancy up to 45% (change can mask hypovolemic shock)

### Shock

- pregnant patients may lose 35% of blood volume without typical signs of shock (i.e. tachycardia, hypotension)
- the fetus may be in "shock" due to contraction of the uteroplacental circulation
- fetal HR changes are an early warning of maternal circulatory compromise

### Management Differences

- place bolster under right hip to stop inferior vena cava compression
- fetal monitoring (HR and fetal movements, continuous tocographic monitoring if viable fetus (>20 wk))
- early obstetrical consult
- do not avoid necessary imaging, but shield as much as possible
- consider need for RhoGAM® if mother Rh negative



The best treatment for the fetus is effective treatment of the mother.

- **Primary survey:** focus on mother
- **Secondary survey:** detailed assessment of mother + acquire info about fetus (Hx, fetal monitoring, etc.)

# Approach to Common ER Presentations

## Abdominal Pain

### Rule Out Life-Threatening Causes

- CVS: MI, aortic dissection (tearing pain), ruptured AAA
- GI: perforated viscus, hepatic/splenic injury, ischemic bowel (diffuse pain)
- gynecologic: ectopic pregnancy

### Additional Differential Diagnosis

- GI: appendicitis, diverticulitis, bowel obstruction, hepatitis, cholecystitis, pancreatitis
- urinary: pyelonephritis, ureteral calculi, cystitis
- genital
  - female: tubo-ovarian abscess, ovarian torsion, ovarian cyst, salpingitis, pelvic inflammatory disease (PID), endometriosis
  - male: testicular torsion, epididymitis, prostatitis
- other: diabetic ketoacidosis (DKA), herpes zoster virus (HZV), intra-abdominal abscess, pneumonia, lead poisoning, porphyria, sickle cell crisis, psychiatric

### History

- pain: OPQRST
- broad differential, including GU, gyne, GI, respiratory, and CV systems
- recent/remote abdominal trauma/surgeries

### Physical Examination

- vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and CVS as indicated by history

### Investigations

- do not delay consultation if patient unstable
- CBC, electrolytes, glucose, BUN/creatinine, U/A,  $\pm$  LFTs, lipase (if upper abdominal pain)  $\pm$  others if indicated:  $\beta$ -hCG, ECG, troponins
- AXR: look for calcifications, free air, gas pattern, air fluid levels
- CXR upright: look for pneumoperitoneum (free air under diaphragm)
- U/S: biliary tract, ectopic pregnancy, AAA, free fluid
- CT: trauma, AAA, pancreatitis, nephro/urolithiasis, appendicitis and diverticulitis

### Management

- NPO, IV, NG tube, analgesics, consider antibiotics and anti-emetics
- growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: general surgery, vascular, gynecology, etc.

### Disposition

- admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develop

## Acute Pelvic Pain

### Etiology

- gynecological
  - 2nd most common gynecological complaint (after vaginal bleeding)
  - ovaries: ruptured ovarian cysts (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass)
  - fallopian tubes: salpingitis (STI), tubal abscess, hydrosalpinx
  - uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in pregnant patient (degeneration), PID, endometriosis
  - other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), dysmenorrhea and endometriosis
- non-gynecological
  - GI: appendicitis, constipation, bowel obstruction, gastroenteritis, diverticulitis, IBD, IBS
  - GU: cystitis, pyelonephritis, ureteric stone
  - other: porphyria, abdominal angina, aneurysm, hernia, zoster



#### Red Flags

- Unstable vital signs
- Fever
- Signs/symptoms of shock
- Rapid onset severe pain



Be vigilant in those at extremes of ages (very young, elderly) as they often present atypically!



#### Abdominal Assessment in all 4 Quadrants

##### DR. GERM

Distention  
Rigidity  
Guarding  
Evisceration/Ecchymosis  
Rebound tenderness  
Masses



If elevated AST and ALT:  
think hepatocellular injury  
AST > ALT: alcohol – related  
ALT > AST: viral, drug, toxin

If elevated ALP and GGT:  
“think biliary tree” stones



Old age, pregnancy (T3), and chronic corticosteroid use can blunt peritoneal findings, so have increased suspicion of intrabdominal process in these individuals!



Unstable patients should not be sent for imaging.



All women of childbearing age are assumed to be pregnant. Every pregnancy is potentially ectopic. A  $\beta$ -hCG must be obtained!



#### Gynecological Causes of Pelvic Pain:

- Ovarian cyst
- Dysmenorrhea
- Mittelschmerz
- Endometriosis
- Ovarian torsion
- Uterine fibroids/neoplasm
- Adnexal neoplasm
- PID + cervicitis



## History and Physical Exam

- pain: OPQRST
- associated symptoms: vaginal bleeding, bowel or bladder symptoms, radiation
- vitals
- gynecological exam: assess for cervical motion tenderness = chandelier sign (suggests PID)
- abdominal exam

## Investigations

- bloodwork
  - $\beta$ -hCG for all women of childbearing age
  - CBC and differential, electrolytes, glucose, BUN/Cr, G&S, PTT/INR
- imaging
  - pelvic and abdominal U/S: evaluate adnexa, look for free fluid in the pelvis or masses, evaluate thickness of endometrium, confirm intrauterine pregnancy if  $\beta$ -hCG positive
  - doppler flow studies for ovarian torsion

## Management

- general: analgesia, determine if admission and consults needed
  - gynecology consult if history and physical suggestive of serious cause
  - other consults as indicated
- specific:
  - ovarian cysts
    - ♦ unruptured or ruptured and hemodynamically stable: analgesia and follow-up
    - ♦ ruptured with significant hemoperitoneum: may require surgery
  - ovarian torsion: surgical detorsion or removal of ovary
  - uncomplicated leiomyomas, endometriosis and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  - PID: requires broad spectrum antibiotics

## Disposition

- admission: patients requiring surgery, IV antibiotics/pain management
- discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

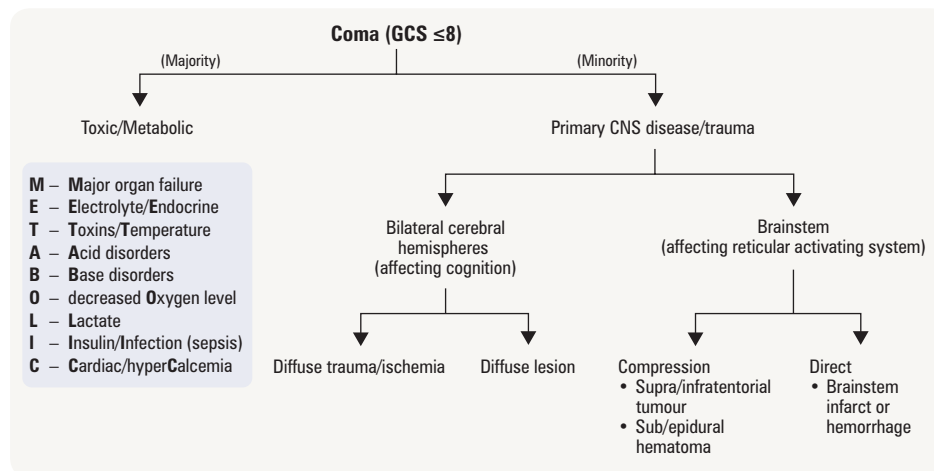


Ultrasound is the preferred imaging modality in the assessment of acute pelvic pain.

## Altered Level of Consciousness (LOC)

### Definitions

- altered mental status: collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness, including:
  - delirium (see [Psychiatry](#), PS19)
  - dementia (see [Psychiatry](#), PS20)
  - lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  - stupor: unresponsiveness but aroused
  - coma: a sleep-like state, not arousable to consciousness
  - use the GCS to evaluate LOC (see *Initial Patient Assessment/Management*, ER2)



### Possible Causes of Coma

#### AEIOU TIPS

Acidosis/Alcohol  
 Epilepsy  
 Infection  
 Oxygen (hypoxia)/Opiates  
 Uremia  
 Temperature/Trauma (especially head)  
 Insulin (too little or too much)  
 Psychogenic/Poisoning  
 Stroke



In general, GCS under 8, intubate, but ability to protect airway is primary consideration!

Figure 10. Etiology of coma

## MANAGEMENT OF ALTERED LOC

### History

- obtain collateral from family, friends, police, paramedics, old chart, etc.
- onset and progression
  - abrupt onset suggests CNS hemorrhage/ischemia or cardiac cause
  - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- preceding events
  - it is essential to determine patient's baseline LOC preceding deterioration
  - antecedent trauma, seizure activity, fever
- past medical history (e.g. similar episode, depression, overdose)

### Physical Examination

- ABCs, vitals including temperature, cardiac, chest, respiratory, abdominal exam, and the "five Ns" (see sidebar)
- complete neuro exam, in particular examination of the eyes (pupil size and reactivity), look for MedicAlert® bracelet

### Investigations

- bloodwork
  - rapid blood sugar, CBC, electrolytes, Cr, BUN, LFTs, glucose, serum osmolality, VBG, PT/PTT/INR, troponins
  - serum EtOH, acetaminophen and salicylate levels
- imaging
  - CXR, CT head
- other tests
  - ECG, U/A, UTox

### Diagnosis

- administer appropriate universal antidotes
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished
  - one ampule D50W IV if low blood sugar on finger-prick
  - naloxone 0.4-2 mg IV or IM if opiate overdose suspected
- distinguish between structural and toxic-metabolic coma
  - structural coma
    - ♦ pupils, extraocular movements and motor findings, if present, are usually asymmetric
    - ♦ look for focal or lateralizing abnormalities
  - toxic-metabolic coma
    - ♦ dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
    - ♦ respiratory depression in association with an intact upper brainstem (e.g. equal and reactive pupils; see exceptions in Table 12)
    - ♦ extraocular movements and motor findings are symmetric or absent
- essential to re-examine frequently – status can change rapidly
- diagnosis may become apparent only with the passage of time
  - delayed deficit after head trauma suggestive of epidural hematoma (characteristic "lucid interval")

**Table 12. Toxic-Metabolic Causes of Fixed Pupils**

Dilated	Dilated to Normal	Constricted
Anoxia	Hypothermia	Cholinergic agents (e.g. organophosphates)
Anticholinergic agents (e.g. atropine, TCAs)	Barbiturates	Opiates (e.g. heroin), except meperidine
Methanol (rare)	Antipsychotics	
Cocaine		
Opioid withdrawal		
Amphetamines		
Hallucinogens		

### Disposition

- admission: if ongoing decreased LOC; admit to service based on tentative diagnosis or transfer patient if appropriate level of care not available
- discharge: readily reversible alteration of LOC; ensure adequate follow-up care available



#### Evaluation of Comatose Patient

##### Five Ns

**Noggin** (Signs of Basal skull fracture)  
e.g. raccoon eyes and Battle's sign (bruising of the mastoid process)  
appears about 8 h after trauma

##### Neck

C-spine, neurogenic shock, nuchal rigidity

##### ENT

Otorrhea, rhinorrhea, tongue biting (Stroke), odour on breath (DKA, hepatic encephalopathy, EtOH), hemotympanum

##### Needles

Inspect for track marks

##### Neurological

Concentrate on GCS, respiration, posture, movement, pupils, reflexes



## Chest Pain

### Rule Out Life-Threatening Causes

- CVS: acute coronary syndrome, pericarditis, cardiac tamponade, aortic dissection
- respiratory: pulmonary embolism (PE), pneumothorax (tension or spontaneous)
- GI: esophageal rupture, pneumomediastinum

### Additional Differential Diagnosis

- cardiac: stable angina
- respiratory: pneumonia
- GI: peptic ulcer disease (PUD), pancreatitis, cholecystitis, esophagitis, reflux, esophageal spasm
- MSK: rib fractures, costochondritis, zoster, etc.
- psychogenic/anxiety (diagnosis of exclusion)

### Initial Resuscitation and Management

- O<sub>2</sub>, IV, cardiac monitoring, CXR (portable if unstable), ECG

### History

- must evaluate cardiac risk factors (see *TIMI Score*, [Cardiology](#), C24)
- classic presentations (but presentation seldom classic)
  - aortic dissection: syncope with sudden severe tearing pain, often radiating to back, ± focal pain/neurologic loss in extremities secondary to major vessel ischemia
  - pulmonary embolism: pleuritic chest pain (75%), dyspnea, anxiety, tachycardia, PERC Score
  - pericarditis: anterior precordial pain, pleuritic, relieved by sitting up and leaning forward
  - acute coronary syndrome (ACS): retrosternal squeezing/pressure pain, radiation to arm/neck, dyspnea, nausea/vomiting, syncope
  - esophageal: frequent heartburn, acid reflux, dysphagia, relief with antacids
- ACS more likely to be atypical in females, diabetics, and >80 yr

### Physical Examination

- vitals (BP in both arms, but unreliable indicator of dissection)
- palpate chest wall for tender points; present in 25% of acute MI, but may suggest MSK cause if symptoms fully reproduced and all serious etiologies have been ruled out
- cardiac exam, respiratory exam, peripheral vascular exam

### Investigations

- bloodwork
  - CBC, electrolytes, BUN/Cr
  - CK-MB: if normal, does not rule out MI
  - troponin I: more sensitive (but positive later than CK-MB; can have false positives in renal failure, must follow for 8 h post onset of symptoms)
  - D-dimer: if negative, can rule out PE in low probability patients (see sidebar)
- ECG (see Table 13)
  - always compare with previous
  - PE and acute MI may have normal ECG in up to 50% of cases
  - consider 15-lead ECG if hypotensive or if ECG shows inferior MI or AV node involvement
- CXR
  - always compare with previous
  - PE (see *DVT*, ER33)
    - ♦ 50% completely normal
    - ♦ atelectasis, elevated hemidiaphragm, pleural effusion
  - aortic dissection (see sidebar ER12 for features)
    - ♦ change from previous CXR is the most accurate finding
    - ♦ widened mediastinum (most consistent finding)
    - ♦ CXR is normal in 20% of thoracic dissections
  - pneumothorax (PTX)
    - ♦ may need inspiration and expiration views
    - ♦ if large, may see tracheal shift (away from tension PTX, towards a non-tension PTX)
- V/Q scan or CT, venous leg Doppler, required to rule out PE in patients with intermediate or high probability (see sidebar for Wells' Score, E34)

### Disposition

- admission and monitoring: patients at risk of developing dysrhythmias
- consult: cardiology for patients with ACS; cardiothoracic surgery for patients with valvular lesions, esophageal rupture, or aortic dissection
- discharge: patients with a low probability of life-threatening illness due to resolving symptoms and negative workup; instruct the patient to return if they develop SOB or increased chest pain



#### Life Threatening Causes of Chest Pain

##### PET MAP

Pulmonary embolism  
Esophageal rupture  
Tamponade  
MI/angina  
Aortic dissection  
Pneumothorax



Imaging is necessary for all suspected aortic dissections, regardless of blood pressure.



#### Signs and Symptoms of MI

##### PULSE

Persistent chest pain  
Upset stomach  
Lightheadedness  
Shortness of breath  
Excessive sweating



#### Signs of PE on CXR

**Westermark's sign:** abrupt tapering of a vessel on chest film.

**Hampton's hump:** a wedge-shaped infiltrate that abuts the pleura.

**Table 13. Common Life Threatening ECG Changes**

Pathology	ECG Findings
<b>Dysrhythmia</b>	
a) Torsade de pointes	Ventricular complexes in upward-pointing and downward-pointing continuum (250-350 bpm)
b) Ventricular tachycardia	6 or more consecutive premature ventricular beats (150-250 bpm)
c) Ventricular flutter	Smooth sine wave pattern of similar amplitude (250-350 bpm)
d) Ventricular fibrillation	Erratic ECG tracing, no identifiable waves
<b>Conduction</b>	
a) 2nd degree heart block (Mobitz Type II)	PR interval stable, some QRS's dropped
b) 3rd degree heart block	Total AV dissociation, but stable P-P and R-R intervals
c) Left bundle branch block	Prolonged QRS complex (> 0.12 s) RSR' in V5 or V6 Monophasic I and V6 May see ST elevation Difficult to interpret, new LBBB is considered STEMI equivalent
<b>Ischemia</b>	
a) STEMI	ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression)
<b>Metabolic</b>	
a) Hyperkalemia	Tall T waves P wave flattening QRS complex widening and flattening
b) Hypokalemia	U waves appear Flattened T waves
<b>Digitalis Toxicity</b>	
	Gradual downward curve of ST At risk for AV blocks and ventricular irritability
<b>Syndromes</b>	
a) Brugada	RBBB with ST elevation in V1, V2 and V3 Susceptible to deadly dysrhythmias, including ventricular fibrillation
b) Wellens	Marked T wave inversion in V2 and V3 Left anterior descending coronary stenosis
c) Long QT syndrome	QT interval longer than 1/2 of cardiac cycle Predisposed to ventricular dysrhythmias

**ACUTE MYOCARDIAL INFARCTION**

- see [Cardiology](#), C24

**Management**

- immediate stabilization
  - oxygen 4 L/min
  - IV access
  - cardiac monitors
  - STAT ECG
  - cardiac enzymes (CK, troponins)
- ASA 162-325 mg chewed
- nitroglycerin 0.3 mg SL q5min x 3 (IV for CHF, HTN, unresolved pain)
- morphine 2-5 mg IV q5-30min if unresponsive to nitroglycerin
- low molecular weight heparin 1 mg/kg SC bid (30 mg IV STAT post TNK infusion)
- thrombolytics (within 30 min) or primary percutaneous coronary intervention (PCI) (within 90 min)
  - agents include rt-PA, streptokinase, and TNK
  - evaluate indications and contraindications prior to use
- other: antidysrhythmics, cardioversion, defibrillation, transthoracic pacing, angioplasty
- cardiology consult



Important to look for reciprocal changes in STEMI in order to differentiate from pericarditis (diffuse elevations).

**Immediate Treatment of Acute MI****BEMOAN**

**β**-Blockade

Enoxaparin

Morphine

Oxygen

ASA

Nitroglycerin



**Addition of Clopidogrel to Aspirin® and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation**  
*NEJM* 2005;352:1179-1191

**Purpose:** To assess the benefit of adding clopidogrel to Aspirin® and fibrinolytic therapy in ST-elevation MI.

**Study Characteristics:** Double-blind, RCT, following intention-to-treat analysis, with 3491 patients and clinical follow-up at 30 d.

**Participants:** Individuals presenting within 12 h of onset of ST-elevation MI (mean age 57, 80.3% male, 50.3% smokers, 9.1% previous MI). Those presenting after 12 h, age >75, or with previous CABG were excluded.

**Intervention:** Clopidogrel (300 mg loading dose followed by 75 mg OD until day of angiogram) or placebo, in addition to Aspirin®, a fibrinolytic agent, and heparin when appropriate.

**Primary Outcome:** Composite of occluded infarct-related artery on angiography (thrombosis in MI flow grade 0 or 1), or death or recurrent MI prior to angiography.

**Results:** Rates of primary end point were 21.7% in the placebo group and 15.0% in the clopidogrel group (95% CI, 24-47%). Among the individual components of the primary end point, clopidogrel had a significant effect on the rate of an occluded infarct-related artery and the rate of recurrent MI, but no effect on the rate of death from any cause. At 30 d clinical follow-up, there was no difference in rate of death from cardiovascular causes, a significant reduction in the odds of recurrent MI, and a non-significant reduction in recurrent ischemia with need for urgent revascularization. The rates of major bleeding and intracranial hemorrhage were similar between the two groups.

**Conclusion:** Addition of clopidogrel improves the patency rate of infarct-related arteries and reduces ischemic complications, both of which are associated with improved long-term survival after MI. The trial was not powered to detect a survival benefit and none was seen.



Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack.

**Complications of Nasal Packing**

- Hypoxemia
- Toxic-shock syndrome
- Aspiration
- Pharyngeal fibrosis/stenosis
- Alar/septal necrosis

**Epistaxis**

- see [Otolaryngology](#), OT26
- 90% of nosebleeds stem from the anterior nasal septum (at Kiesselbach's plexus located in Little's area)
- can be life-threatening

**Etiology**

- most commonly caused by trauma (digital, blunt, foreign bodies)
- other causes: barometric changes, nasal dryness, chemicals (cocaine, Otrivin®), or systemic disease (coagulopathies, hypertension, etc.)

**Investigations**

- bloodwork: CBC, PT/PTT (as indicated)
- imaging: x-ray, CT as needed



## Treatment

- aim is to localize bleeding and achieve hemostasis
- first-aid: ABCs, lean forward, pinch cartilaginous portion of nose for 20 min twice
- assess blood loss: vitals, IV normal saline, cross match 2 units packed RBC if significant
- determine site of bleeding: use topical anaesthetic/vasoconstrictor to facilitate; use nasal speculum and good lighting
- attempt to control the bleeding
  - first line: Otrivin® or cocaine
  - second line: cauterize with silver nitrate (one side of septum only because if both are cauterized this can lead to septal perforation!)
  - if these fail, or if bleeding is posterior → nasal packing (must monitor for complications)
  - if packing fails, consult ENT

## Disposition

- discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. humidifiers, saline spray, topical ointments, avoiding irritants, managing hypertension)
- admission: severe cases of refractory bleeding

# Headache

- see also [Neurology](#), N38

## Etiology

- the common
  - common migraine (no aura)/classic migraine (involves aura)
    - ♦ gradual onset, unilateral/bilateral, throbbing
    - ♦ nausea/vomiting, photo/phonophobia
    - ♦ treatment: analgesics, neuroleptics, vasoactive meds
  - tension/muscular headache
    - ♦ never during sleep, gradual over 24 h
    - ♦ posterior/occipital
    - ♦ increased with stressors
    - ♦ treatment: modify stressor, local measures, NSAIDs, tricyclic antidepressants
- the deadly
  - subarachnoid hemorrhage (SAH) (see [Neurosurgery](#), NS18)
    - ♦ sudden onset, increased with exertion
    - ♦ reaches maximum intensity within minutes, nausea and vomiting, meningeal signs
    - ♦ diagnosis: CT, LP (5-10% of patients with SAH have negative initial CT)
      - sensitivity of CT decreases with time and is much less sensitive by 48-72 h
      - if CT done within 6 h of headache onset, no need for LP
    - ♦ management: urgent neurosurgery consult
  - increased ICP
    - ♦ worse in morning, when supine or bending down, with cough or Valsalva
    - ♦ physical exam: neurological deficits, cranial nerve palsies, papilledema
    - ♦ diagnosis: CT scan
    - ♦ management: consult neurosurgery
  - meningitis (see [Infectious Diseases](#), ID19)
    - ♦ flu-like presentation initially (fever, nausea/vomiting, malaise), meningeal signs, purpuric rash
    - ♦ altered LOC and confusion
    - ♦ perform CT to rule out increased ICP then do LP for diagnosis
    - ♦ treatment: early empiric antibiotics (depending on age group), steroid therapy
  - temporal arteritis (causes great morbidity in terms of blindness) (see [Ophthalmology](#), OP38)
    - ♦ unilateral scalp tenderness, jaw claudication, visual disturbances
    - ♦ labs: elevated ESR, CRP
    - ♦ temporal artery biopsy is gold standard for diagnosis
    - ♦ associated with polymyalgia rheumatica
    - ♦ treatment: high-dose steroids immediately if suspected

## Disposition

- admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications
- discharge: most patients can be discharged with appropriate analgesia and follow up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain



Note: up to 5% of patients with subarachnoid hemorrhage have a normal CT scan; if suspect SAH with a negative CT, perform a LP.



### DDx Subarachnoid Hemorrhage

#### BATS

Berry aneurysm  
Arteriovenous malformation/Adult polycystic kidney disease  
Trauma  
Stroke



### Meningitis

Do not delay IV antibiotics for LP.



## Joint Pain

- see [Rheumatology](#), RH3

### Rule Out Life-Threatening Causes

- septic joint (see [Orthopedics](#), OR10)

### Differential Diagnosis

- articular pain
  - monoarticular
    - ♦ infectious: bacterial, viral, fungal
    - ♦ hemarthrosis: trauma/fracture, anticoagulants, bleeding diatheses
    - ♦ crystal induced: gout, calcium pyrophosphate deposition, hydroxyapatite
    - ♦ inflammatory: seropositive, seronegative
    - ♦ neoplasm
    - ♦ degenerative: osteoarthritis
  - polyarticular
    - ♦ infectious: Lyme disease, bacterial endocarditis, septicemia, gonococcus, viral
    - ♦ post-infectious: rheumatic fever, reactive arthritis, enteric infections
    - ♦ inflammatory: seropositive, seronegative
    - ♦ degenerative: osteoarthritis
- non-articular
  - musculoskeletal
    - ♦ localized: tendonitis, bursitis, capsulitis, muscle sprain
    - ♦ generalized: fibromyalgia, polymyalgia rheumatica
- other
  - neurologic: spinal stenosis/spondylolithesis, degenerative disc disease, cauda equina syndrome, neoplasm, thoracic outlet syndrome, Charcot joint
  - vascular: intermittent claudication

### History and Physical Examination

- associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
- patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
- inflammatory symptoms: prolonged morning stiffness, stiffness and pain ease through the day, midday fatigue, soft tissue swelling
- non-inflammatory symptoms: stiffness short lived after inactivity, short duration stiffness in the morning, pain increases with activity
- assess ROM, presence of joint effusion, warmth
- watch for: localized joint pain, erythema, warmth, swelling with pain on active ROM, inability to bear weight, fever as these may indicate presence of septic joint

### Investigations

- bloodwork
  - CBC, ESR, CRP, WBC, INR/PTT, blood cultures, urate
- imaging
  - joint x-ray ± contralateral joint for comparison
- other investigations
  - joint aspirate → send for: WBC, protein, glucose, Gram stain, crystals

### Management

- septic joint: IV antibiotics ± joint decompression and drainage
  - antibiotics can be started empirically if septic arthritis cannot be ruled out
- crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids
  - do not use allopurinol, as it may worsen acute attack
- acute polyarthritis: NSAIDs, analgesics (acetaminophen ± opioids), local or systemic corticosteroids
- osteoarthritis: NSAIDs, acetaminophen
- soft tissue pain: allow healing with enforced rest ± immobilization
  - nonpharmacologic treatment: local heat or cold, electrical stimulation, massage
  - pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents



#### Causes of Joint Pain

##### SOFTER TISSUE

Sepsis  
Osteoarthritis  
Fractures  
Tendon/muscle  
Epiphyseal  
Referred  
  
Tumour  
Ischemia  
Seropositive arthritides  
Seronegative arthritides  
Urate  
Extra-articular rheumatism  
(e.g. polymyalgia)



#### Hospitalization is required for joint pain in the presence of:

- Significant, concomitant internal organ involvement
- Signs of bacteremia, including vesiculopustular skin lesions, Roth spots, shaking chills, or splinter hemorrhages
- Systemic vasculitis
- Severe pain
- Severe constitutional symptoms
- Purulent synovial fluid in one or more joints
- Immunosuppression

## Otalgia

### Differential Diagnosis (see also [Otolaryngology](#), OT6)

- local
  - infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis in diabetics, herpes simplex/zoster, auricular cellulitis, external canal abscess
  - others: trauma, neoplasm, foreign body, cerumen impactions, granulomatosis with polyangiitis





**History**

- OPQRST
- associated symptoms: aural fullness (feeling of pressure), otorrhea, hearing loss, tinnitus, vertigo, pruritis, fever
- risk factors: Q-tip use, hearing aids, headphones

**Physical Exam**

- observe for otorrhea, palpation of outer ear/mastoid, otoscope to see bulging erythematous TM, perforation

**Investigations**

- consider audiogram if hearing loss
- CT head if suspicion of mastoiditis, malignant OM

**Management**

- debridement and antibiotics for cerumen and infection

## Seizures

- see [Neurology](#), N14

**Definition**

- paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons

**Categories**

- generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
- partial seizure (focal): simple partial, complex partial
- causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP), metabolic disturbance (hypo/hyperglycemia, hypo/hyponatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
- differential diagnosis: syncope, pseudoseizures, migraines, movement disorder, narcolepsy/cataplexy, myoclonus

**History**

- from patient and bystander: flaccid and unconscious, often with deep rapid breathing
- preceding aura, rapid onset, loss of bladder/bowel control, tongue-biting (sides of the tongue)
- timing: length of seizure

**Physical Examination**

- injuries to head and spine and bony prominences (e.g. elbows), tongue laceration, aspiration, urinary incontinence

**Investigations**

- known seizure disorder: anticonvulsant levels
- Accu-Chek®
- first time seizure: CBC, serum glucose, electrolytes, BUN/Cr,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ; consider prolactin,  $\beta$ -hCG, toxicology screen
- initial imaging: CT; x-ray if suspected extremity injuries. Definitive imaging: MRI, EEG


**Minimum Workup in an Adult with 1st Time Seizure**

CBC and differential  
Electrolytes including  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{PO}_4^{3-}$   
Head CT

**Table 14. Management of Status Epilepticus**

Time (min)	Steps
0-5	Give oxygen; ensure adequate ventilation Monitor: vital signs, electrocardiography, oximetry Establish IV access; obtain blood samples for glucose level, CBC, electrolytes, toxins, and anticonvulsant levels
6-9	Give 50 mL 50% glucose (preceded by thiamine 100 mg IM in adults)
10-20	IV lorazepam 0.1 mg/kg at 2 mg/min or IV diazepam 0.2 mg/kg at 5 mg/min Diazepam can be repeated if seizures do not stop after 5 min; if diazepam is used to stop the status, then phenytoin should be administered promptly to prevent the recurrence of status
21-60	If status persists, administer 15-20 mg/kg of phenytoin intravenously no faster than 50 mg/min in adults and 1 mg/kg/min in children
>60	If status does not stop after 20 mg/kg of phenytoin, give additional doses of 5 mg/kg to a maximal dose of 30 mg/kg If status persists, then give 20 mg/kg of phenobarbital IV at 100 mg/min. When phenobarbital is given after a benzodiazepine, ventilatory assistance is usually required If status persists, then give general anaesthesia (e.g. pentobarbital). Vasopressors or fluid volume are usually necessary. Electroencephalogram should be monitored. Neuromuscular blockade may be needed



If administering phenytoin, patient must be on a cardiac monitor as dysrhythmias and/or hypotension may occur.

**Disposition**

- the decision to admit or discharge should be based on the underlying disease process identified
  - if a patient has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
- first-time seizure patients being discharged should be referred to a neurologist for follow-up
- admitted patients should generally have a neurology consult
- patient should not drive until medically cleared (local regulations vary)
  - complete notification form to appropriate authority re: ability to drive
- warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)

## Shortness of Breath

- see [Respirology](#), R3 and [Cardiology](#), C5

**Etiology**

- categorized into one of two groups: respiratory or cardiovascular
- respiratory system dyspnea: discomfort related to disorders of the central controller (brain), the ventilatory pump (ventilatory muscles, peripheral nerves), and the gas exchanger (alveoli and pulmonary capillaries)
- cardiovascular system dyspnea: cardiac diseases (acute ischemia, heart failure, systolic dysfunction, valvular disorders, pericardial diseases, arrhythmias), anemia, and deconditioning

**History/Physical**

- acute SOB is often due to a relatively limited number of conditions. Associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischemia
  - fever, cough and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
- dyspnea may be the sole complaint and the physical examination may reveal few abnormalities (e.g. pulmonary embolism, pneumothorax)
- chest tightness may be indicative of bronchospasm
- a sensation of rapid, shallow breathing may correspond to interstitial disease
- a sense of heavy breathing is typical of deconditioning
- vitals including pulse oximetry
  - wheeze (airway) vs. crackles (parenchymal), JVP, and murmurs

**Investigations**

- bloodwork
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider VBG
  - serial cardiac enzymes and ECG if considering cardiac source
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection or interstitial fluid)
  - CT chest usually is not indicated in the initial evaluation of patients with dyspnea, but can be valuable in patients with interstitial lung disease, occult emphysema, or chronic thromboembolic disease (PE)

**Disposition**

- the history and physical examination lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified
  - consider intubation in CO<sub>2</sub> retainers (e.g. COPD)
- if the decision to discharge is chosen, provide appropriate discharge instructions to return in case of returning/worsening SOB

## Syncope

**Definition**

- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system hypoperfusion

**Etiology**

- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, tamponade, tension pneumothorax, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)

**Causes of Acute Dyspnea**

**Cardiovascular:** acute MI, CHF, cardiac tamponade, arrhythmias.

**Respiratory:** bronchospasm, pulmonary embolism, pneumothorax, infection (bronchitis, pneumonia), upper airway obstruction (aspiration, anaphylaxis).

**5 Types of Syncope**

- Vasomotor
- Cardiac
- CNS
- Metabolic
- Psychogenic

## History

- gather details from witnesses, and clarify patient's experience (e.g. dizziness, ataxia, or true syncope)
  - two key historical features 1. Prodrome 2. Situation
- distinguish between syncope and seizure (see [Neurology](#), N15)
  - some patients may have myoclonic jerks with syncope – NOT a seizure
  - signs and symptoms during presyncope, syncope and postsyncope
  - past medical history, drugs
  - think anatomically in differential: pump (heart), blood, vessels, brain
- syncope is cardiogenic until proven otherwise if:
  - there is sudden loss of consciousness with no warning or prodrome OR
  - syncope is accompanied by chest pain

## Physical Examination

- postural BP and HR
- cardiovascular, respiratory and neuro exam
- physical findings in the elderly patient who falls (**I HATE FALLING**):
  - Inflammation of joints (or joint deformity)
  - Hypotension (orthostatic blood pressure changes)
  - Auditory and visual abnormalities
  - Tremor (Parkinson's disease or other causes of tremor)
  - Equilibrium (balance) problem
  - Foot problems
  - Arrhythmia (dysrhythmia), heart block or valvular disease
  - Leg-length discrepancy
  - Lack of conditioning (generalized weakness)
  - Illness
  - Nutrition (poor; weight loss)
  - Gait disturbance

## Investigations

- ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval), bedside glucose
- bloodwork: CBC, electrolytes, BUN, creatinine, ABGs, troponin,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\beta\text{-hCG}$
- consider toxicology screen

## Management

- ABCs, IV,  $\text{O}_2$ , monitor
- examine for signs of trauma caused by syncopal episode
- cardiogenic syncope: admit to medicine/cardiology
- low risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

## Disposition

- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow up with family physician
  - educate re: avoiding orthostatic or situational syncope
  - patients with recurrent syncope should avoid high-risk activities (e.g. driving)



### Causes of Syncope by System

#### HEAD, HEART, VeSSELS

Hypoxia/Hypoglycemia

Epilepsy

Anxiety

Dysfunctional brainstem

Heart attack

Embolism (PE)

Aortic obstruction

Rhythm disturbance

Tachycardia

Vasovagal

Situational

Subclavian steal

ENT (glossopharyngeal neuralgia)

Low systemic vascular resistance

Sensitive carotid sinus



**San Francisco Syncope Rule: High risk of adverse outcomes in syncope patients if:**

#### CHES

CHF: Hx of CHF

Hct: Low

ECG: Abnormal

SOB: Hx of dyspnea

SBP: SBP <90 at triage



**Which patients with syncope should be admitted?**

Those at risk of complications:

- Older than 60-70 yr
- Significant cardiac risk factors
- Recurrent syncope
- Serious underlying illness



## Sexual Assault

- legally required to report sexual assault if victim is <16 yr of age to Children's Aid Society (CAS)

## Epidemiology

- 1 in 4 women and 1 in 10 men will be sexually assaulted in their lifetime
- it is estimated that only 7% of rapes are reported

## General Approach

- ABCs, treat acute, serious injuries
- ensure patient is not left alone and provide ongoing emotional support
- set aside adequate time for exam (usually 1.5 h)
- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained)
- Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests (legally required if <16 yr old)



Legally required to report sexual assault if victim is <16 yr of age to Children's Aid Society (CAS).

**History**

- ensure privacy for the patient – others should be asked to leave
- questions to ask: who? when? where did penetration occur? what happened? any weapons or physical assault?
- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
  - gravity, parity, last menstrual period
  - contraception use
  - last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

**Physical Examination**

- evidence collection is always secondary to treatment of serious injuries
- never re-traumatize a patient with the examination
- general examination
  - mental status
  - sexual maturity
  - patient should remove clothes and place in paper bag
  - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
- pelvic exam and specimen collection
  - ideally before urination or defecation
  - examine for seminal stains, hymen, signs of trauma
  - collect moistened swabs of dried seminal stains
  - pubic hair combings and cuttings
  - speculum exam
    - ♦ lubricate with water only
    - ♦ vaginal lacerations, foreign bodies
    - ♦ Pap smear
    - ♦ oral/cervical/rectal culture for gonorrhea and chlamydia
    - ♦ posterior fornix secretions if present or aspiration of saline irrigation
    - ♦ immediate wet smear for motile sperm
    - ♦ air-dried slides for immotile sperm, acid phosphatase, ABO group
- others
  - fingernail scrapings
  - saliva sample from victim

**Investigations**

- VDRL: repeat in 3 mo if negative
- serum  $\beta$ -hCG
- blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

**Management**

- involve local/regional sexual assault team
- medical
  - suture lacerations
  - tetanus prophylaxis
  - gynecology consult for foreign body, complex lacerations
  - assumed positive for gonorrhea and chlamydia
    - ♦ management: azithromycin 1 g PO x 1 dose (alt: doxycycline 100 mg PO bid x 7 d) and cefixime 800 mg PO x 1 dose
  - may start prophylaxis for hepatitis B and HIV
  - pre and post counselling for HIV testing
  - pregnancy prophylaxis offered
    - ♦ levonorgestrel 0.75 mg PO STAT, repeat within 12 h (Plan B\*)
- psychological
  - high incidence of psychological sequelae
  - have victim change and shower after exam completed

**Disposition**

- discharge if injuries/social situation permit
- follow-up with MD in rape crisis centre within 24 h
- best if patient does not leave ED alone

**DOMESTIC VIOLENCE**

- women are usually the victims, but male victimization also occurs
- identify the problem (need high index of suspicion)
  - suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns or other injuries; often do not match up with history provided)
  - somatic symptoms (chronic and vague complaints)
  - psychosocial symptoms
  - clinician impression (your 'gut feeling', e.g. overbearing partner that won't leave patient's side)

**Risk of Sexually Transmitted Disease After Sexual Assault**

- Gonorrhea: 6-18%
- Chlamydia: 4-17%
- Syphilis: 0.5-3%
- HIV: <1%



How do you get a patient who is accompanied by her partner alone without arousing suspicion? Order an x-ray.

- if disclosed, be supportive and assess danger
- if necessary, order an x-ray to get patient alone to question
- patient must consent to follow-up investigation/reporting (unless for children)

### Management

- treat injuries
- ask about sexual assault and children at home (encourage notification of police)
- document findings
- safety plan
- follow-up: family doctor/social worker

## Medical Emergencies



### Anaphylaxis and Allergic Reactions

#### Etiology

- anaphylaxis is an exaggerated immune mediated hypersensitivity reaction that leads to systemic histamine release, increased vascular permeability, and vasodilation. Regardless of the etiology, the presentation and the management of anaphylactic reactions are the same
  - allergic (re-exposure to allergen)
  - non-allergic (e.g. exercise induced)

#### Presentation

- classic presentation of anaphylaxis includes:
  1. rapid onset and progression of symptoms
  2. life threatening compromise of one or more of airway (breathing/swallowing difficulty, stridor, voice change), breathing (shortness of breath, hypoxemia, wheezing, respiratory arrest), and circulation (tachycardia, hypotension, confusion, decreased urine output, chest pain)
  3. involvement of skin (erythema, urticaria, warmth) and/or mucosa (angioedema, obstruction, GI symptoms). Not always present
- most common allergens causing anaphylaxis are food (nuts, seafood), stings, and drugs (antibiotics, anesthetics)
- the presentation of anaphylaxis is diverse and there is no one specific symptom or sign for it
  - combinations of symptoms and signs will make anaphylaxis more likely
- life threatening differentials for anaphylaxis include asthma and septic shock

#### Management

1. immediate initial management (call for help and perform concurrently)
  - give 0.5 mL of 1:1000 epinephrine IM to lateral thigh. (0.01 mL/kg up to 0.4 mL for children)
  - remove causative agent if possible
  - if severely compromised ABC or LOC, consult ICU immediately
  - otherwise, provide 100% Oxygen through mask, give bolus 1000 mL (20 mL/kg for children) crystalloid IV then reassess. If IV access difficult give fluid through intraosseous route
  - have continuous pulse oximetry and telemetry monitoring
  - frequently monitor blood pressure
2. secondary treatment
  - diphenhydramine (Benadryl®) 50 mg IM or IV q4-6h
  - methylprednisolone 50-100 mg IV (dose depending on severity)
  - salbutamol (Ventolin®) via nebulizer if bronchospasm

#### Disposition

- monitor for 4-6 h in ED (minimum) and arrange follow up with family physician in 24-48 h
- can have second phase (biphasic) reaction up to 48 h later, patient may need to be supervised (oral steroids on discharge may prevent this)
- educate patient on avoidance of allergens
- 3-day course of:
  - H1 antagonist (cetirizine 10 mg PO OD or Benadryl® 50 mg PO q4-6h)
  - H2 antagonist (ranitidine 150 mg PO OD)
  - corticosteroid (prednisone 50 mg PO OD) generally given for 5 d



#### Most Common Triggers for Anaphylaxis

- Foods (nuts, shellfish, etc.)
- Stings
- Drugs (penicillin, NSAIDs, ACEI)
- Radiographic contrast media
- Blood products
- Latex



Anaphylaxis should be suspected if airway, breathing or especially circulation compromise is present after exposure to a known allergen.



#### Treatment

- Airway control
- Epinephrine
- Establish IV and give fluids
- Steroids
- Anti-histamines

## Asthma

- see [Respirology](#), R6
- chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction



Beware of the silent asthmatic! This is a medical emergency and may require emergency intubation.

## Investigations

- O<sub>2</sub> saturation
- peak flow meter
- $\pm$  ABG if in severe respiratory distress
- CXR if diagnosis in doubt or concerns of pneumonia, pneumothorax, etc.

**Table 15. Asthma Assessment and Management**

Classifications	History and Physical Examination	Management
<b>Respiratory Arrest Imminent</b>	<ul style="list-style-type: none"> <li>• Exhausted, confused, diaphoretic, cyanotic</li> <li>• Silent chest, ineffective respiratory effort</li> <li>• Decreased HR, RR &gt; 30, pCO<sub>2</sub> &gt; 45 mmHg</li> <li>• O<sub>2</sub> sat &lt; 90% despite supplemental O<sub>2</sub></li> </ul>	<ul style="list-style-type: none"> <li>• 100% O<sub>2</sub>, cardiac monitor, IV access</li> <li>• Intubate (consider induction with ketamine)</li> <li>• <math>\beta</math>-agonist: nebulizer 5 mg continually</li> <li>• Anticholinergics: nebulizer 0.5 mg x 3</li> <li>• IV steroids: methylprednisolone 125 mg</li> </ul>
<b>Severe Asthma</b>	<ul style="list-style-type: none"> <li>• Agitated, diaphoretic, laboured respirations</li> <li>• Speaking in words</li> <li>• No relief from <math>\beta</math>-agonist</li> <li>• O<sub>2</sub> sat &lt; 90%, FEV<sub>1</sub> &lt; 50%</li> </ul>	<ul style="list-style-type: none"> <li>• Anticipate need for intubation</li> <li>• Similar to above management</li> <li>• Magnesium sulphate 2 g IV</li> <li>• O<sub>2</sub> to achieve O<sub>2</sub>-sat &gt; 92%</li> </ul>
<b>Moderate Asthma</b>	<ul style="list-style-type: none"> <li>• SOB at rest, cough, congestion, chest tightness</li> <li>• Speaking in phrases</li> <li>• Inadequate relief from <math>\beta</math>-agonist</li> <li>• FEV<sub>1</sub> 50-80%</li> </ul>	<ul style="list-style-type: none"> <li>• O<sub>2</sub> to achieve O<sub>2</sub>-sat &gt; 92%</li> <li>• <math>\beta</math>-agonist: MDI or nebs q5min</li> <li>• Steroids: prednisone 40-60 mg PO</li> <li>• Anticholinergics (Atrovent) MDI or nebs x3</li> </ul>
<b>Mild Asthma</b>	<ul style="list-style-type: none"> <li>• Exertional SOB/cough with some nocturnal symptoms</li> <li>• Difficulty finishing sentences</li> <li>• FEV<sub>1</sub> &gt; 80%</li> </ul>	<ul style="list-style-type: none"> <li>• <math>\beta</math>-agonist</li> <li>• Monitor FEV<sub>1</sub></li> <li>• Consider steroids (MDI or PO)</li> </ul>

## Disposition

- $\beta$ -agonist MDI regular use (2-4 puffs q2-4h) until symptoms controlled then prn
- prednisone 30-60 mg/d for 7-14 d with no taper
- inhaled corticosteroids
- follow-up with primary care physician



### 5 Essential Elements on History

- Cause of exacerbation
- Previous ER/ICU visits
- Previous intubations
- Timing of recent steroid use
- Frequency of asthma medication use



### Treatment of Asthma

#### ASTHMA

Adrenergics ( $\beta$ -agonists)

Steroids

Hydration

Mask (O<sub>2</sub>)

Antibiotics (if concurrent bacterial pneumonia)

## Cardiac Dysrhythmias

- see [Cardiology](#), C12



### Bradycardias and AV Conduction Blocks

- AV conduction blocks
  - 1<sup>st</sup> degree: prolonged PR interval (>200 msec), no treatment required
  - 2<sup>nd</sup> degree
    - ♦ Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - ♦ Mobitz II: PR interval constant with dropped QRS complex, can progress to 3<sup>rd</sup> degree AV block
  - 3<sup>rd</sup> degree: P wave unrelated to QRS complex, PP and RR intervals constant
    - ♦ atropine and transcutaneous pacemaker (TCP) (atropine with caution)
    - ♦ if TCP fails consider dopamine, epinephrine IV
  - long term treatment for Mobitz II and 3<sup>rd</sup> degree block – internal pacemaker
- sinus bradycardia (rate < 60 bpm)
  - can be normal (especially in athletes)
  - causes: vagal stimulation, vomiting, myocardial infarction/ischemia, increased ICP, sick sinus node, hypothyroidism, drugs (e.g.  $\beta$ -blockers, CCBs)
  - treat if symptomatic (hypotension, chest pain)
    - ♦ acute: atropine  $\pm$  transcutaneous pacing
    - ♦ sick sinus: transcutaneous pacing
    - ♦ drug induced: discontinue/reduce offending drug

### Supraventricular Tachydysrhythmias (narrow QRS)

- sinus tachycardia (rate > 100 bpm)
  - causes: increased sympathetic tone, drugs, fever, hypotension, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause, consider  $\beta$ -blocker if symptomatic
- regular rhythm
  - vagal maneuvers (carotid massage, Valsalva), adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once
  - rhythm converts: probable re-entry tachycardia (AVNRT more common than AVRT)
    - ♦ monitor for recurrence
    - ♦ treat recurrence with adenosine or longer acting medications



If the patient with tachydysrhythmia is unstable, perform immediate synchronized cardioversion.



### Clinical Features of Instability

- Hypotension (sBP < 90)
- CHF or pulmonary edema
- Chest pain
- Altered LOC (may indicate shock)



- rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
  - ♦ rate control (diltiazem,  $\beta$ -blockers) and consult cardiology
- irregular rhythm
  - probable atrial fibrillation, atrial flutter or multifocal atrial tachycardia
  - rate control (diltiazem,  $\beta$ -blockers)

### Atrial Fibrillation (AFib)

- most common sustained dysrhythmia; no organized P waves (atrial rate  $>300/\text{min}$ ), irregularly irregular heart rate, narrow QRS (typically)
- etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, sick sinus syndrome
- treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
- decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
- acute management
  - if unstable: immediate synchronized cardioversion
  - if onset of AFib is  $>48$  h: rate control, anticoagulate 3 wk prior to and 4 wk after cardioversion or do transesophageal echo to rule out clot
  - if onset  $<48$  h: may cardiovert
    - ♦ electrical cardioversion: synchronized direct current (DC) cardioversion
    - ♦ chemical cardioversion: procainamide, flecainide, propafenone
- long term management: rate or rhythm control, consider anticoagulation (CHADS2 score, see sidebar)



If patient has Wolff-Parkinson-White and is in AFib use amiodarone or procainamide. Avoid AV nodal blocking agents (adenosine, digoxin, diltiazem, verapamil,  $\beta$ -blockers) as this can increase conduction through bypass tract leading to cardiac arrest



Use the CHADS2 score from Table 3, [Cardiology, C17](#)

### Ventricular Tachydysrhythmias (wide QRS)

- ventricular tachycardia (VT) (rate usually 140-200 bpm)
  - definition: 3 or more consecutive ventricular beats at  $>100$  bpm
  - etiology: CAD with MI is most common cause
  - treatment: sustained VT ( $>30$  s) is an emergency
    - ♦ hemodynamic compromise: synchronized DC cardioversion
    - ♦ no hemodynamic compromise: synchronized DC cardioversion, lidocaine, amiodarone, procainamide
- ventricular fibrillation: call a code blue, follow ACLS for pulseless arrest
- torsades de pointes
  - looks like VT but QRS 'rotates around baseline' with changing axis and amplitude (twisted ribbon)
  - etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
  - treatment:
    - ♦ IV  $\text{Mg}^{2+}$ , temporary overdrive pacing, isoproterenol
    - ♦ correct cause of prolonged QT

## Chronic Obstructive Pulmonary Disease (COPD)

- see [Respirology, R8](#)
- progressive development of irreversible airway obstruction, typically caused by smoking
- acute exacerbation: episode of increased dyspnea, coughing, increase in sputum volume or purulence

### History and Physical Examination

- worsening dyspnea or tachypnea
- acute change in frequency, quantity and colour of sputum production
- triggers: pneumonia, urinary tract infection, PE, CHF, MI, drugs

### Investigations

- CBC, electrolytes, ABG, CXR, ECG, PFTs

### Management

- keep  $\text{O}_2$  sat 88-92% (beware of  $\text{CO}_2$  retainers, but do not withhold  $\text{O}_2$  if hypoxic)
- apply BiPAP if severe distress, arterial pH  $<7.35$  or hypercapnic
- ipratropium is bronchodilator of choice, add salbutamol
- steroids: prednisone 40 mg PO (tapered over 3 wk)
- antibiotics: TMP-SMX, cephalosporins, respiratory quinolones (if signs of infection)
- ICU admission, if life-threatening, for ventilation (chance of ventilation dependency)
- lower threshold to admit if co-morbid illness

### Disposition

- can use up to 4-6 puffs qid of ipratropium and salbutamol for exacerbations
- continue antibiotics if started and give tapering steroids



#### Need to Rule Out with COPD Exacerbation

- Pneumothorax
- CHF exacerbation
- Acute MI
- Pneumonia and other infectious causes
- PE

## Congestive Heart Failure

- also see [Cardiology](#), C30

### Etiology

- decreased myocardial contractility: ischemia, infarction, cardiomyopathy, myocarditis
- pressure overload states: hypertension, valve abnormalities, congenital heart disease
- restricted cardiac output: myocardial infiltrative disease, cardiac tamponade
- volume overload

### Causes of Exacerbation or Precipitants

- please refer to the FAILURE mnemonic on the side bar

### Presentation

- left-sided heart failure
  - dyspnea, decreased exercise tolerance, paroxysmal nocturnal dyspnea, orthopnea, nocturia, fatigue, possibly altered mental status, syncope, angina, systemic hypotension
  - hypoxia, decreased air entry to lungs, rales, S3 or S4, pulmonary edema (on CXR), pleural effusion (usually right sided)
- right-sided heart failure
  - dependent bilateral pitting edema, JVP elevation, hepatic enlargement, ascites
- patients often present with a combination of right-sided and left-sided symptoms

### Investigations

- labs: CBC, electrolytes, AST, ALT, bilirubin, creatinine, BUN, cardiac enzymes, BNP (brain natriuretic peptide)
- chest x-ray (see sidebar)
- ECG: look for MI, ischemia (ST elevation/depression, T-wave inversion)
  - in CHF: LVH, atrial enlargement, conduction abnormalities
- ABG: if severe or refractory to treatment
  - hypoxemia, hypercapnia and acidosis are signs of severe CHF
- echocardiogram: not usually used in emergency evaluation, previous results may aid in diagnosis
- may be precipitated by dysrhythmia (e.g. sudden onset AFib) – correct if new
- rule out serious differentials such as PE, pneumothorax, pneumonia/empyema, COPD exacerbation

### Management (acute)

- ABC, may require intubation if severe hypoxia
- sit upright, cardiac monitoring and continuous pulse oximetry
- saline lock IV, Foley catheter (to follow effectiveness of diuresis)
- 100% O<sub>2</sub> by mask
  - if poor response may require BiPAP or intubation
- drugs
  - nitroglycerin 0.3 mg SL q5min prn ± topical nitro patch (0.2-0.8 mg/h)
    - ♦ if not responding or ischemia: 10-200 µg/min IV, titrate
  - diuretic if volume overloaded (e.g. furosemide 40-80 mg IV), use caution if cause is valvulopathy
  - morphine 1-2 mg IV prn
    - ♦ if hypotensive: dobutamine (2.5 µg/kg/min IV) or dopamine (5-10 µg/kg/min IV), titrate up to sBP 90-100 mmHg
    - ASA 160 mg chew and swallow
- treat precipitating factor (See side bars for common precipitants)
- cardiology or medicine consult



#### Causes of CHF Exacerbation

##### FAILURE

Forgot medication  
 Arrhythmia (Dysrhythmia)/Anemia  
 Ischemia/Infarction/Infection  
 Lifestyle (e.g. too much salt)  
 Upregulation of cardiac output (pregnancy, hyperthyroidism)  
 Renal failure  
 Embolism (pulmonary)



#### Hospital Management Required if:

- Acute MI
- Pulmonary edema or severe respiratory distress
- Severe complicating medical illness (e.g. pneumonia)
- Anasarca
- Symptomatic hypotension or syncope
- Refractory to outpatient therapy
- Thromboembolic complications requiring interventions
- Clinically significant dysrhythmias
- Inadequate social support for safe outpatient management
- Persistent hypoxia requiring supplemental oxygen



#### CHF on CXR

- Pulmonary vascular redistribution
- Perihilar infiltrates
- Interstitial edema, Kerley B lines
- Alveolar edema, bilateral infiltrates
- May see cardiomegaly, pleural effusions



#### Acute Treatment of CHF

##### LMNOP

Lasix (furosemide)  
 Morphine  
 Nitroglycerine  
 Oxygen  
 Position (sit upright), Pressure (BiPAP)



#### Risk Factors for VTE

##### THROMBOSIS

Trauma, travel  
 Hypercoagulable, HRT  
 Recreational drugs (IVDU)  
 Old (age >60)  
 Malignancy  
 Birth control pill  
 Obesity, obstetrics  
 Surgery, smoking  
 Immobilization  
 Sickness (CHF, MI, nephrotic syndrome, vasculitis)

## DVT and Pulmonary Embolism

- see also [Respirology](#), R17

### Risk Factors

- Virchow's triad
  - alterations in blood flow (venous stasis)
  - injury to endothelium
  - hypercoagulable state (including pregnancy, use of OCP, malignancy)
- clinical risk factors

## Presentation

- DVT: calf pain, leg swelling/erythema/edema, palpable cord on exam; can be asymptomatic
- PE: dyspnea, pleuritic chest pain, hemoptysis, tachypnea, cyanosis, hypoxia, fever
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT/PE; investigation often needed (see Figures 11 and 12)
- calculate the PERC (PE rule out criteria) score to assess the need for PE work-up before assessing the likelihood of a PE (Wells criteria)

## Investigations (see Figures 11, 12 and 13)

- ECG and CXR are useful to look for other causes (e.g. ACS, pneumonia)
- D-dimer is only useful if it is negative in low risk patients (highly sensitive)
- ultrasound has high sensitivity and specificity for proximal clot but only 73% sensitivity for DVT below the knee (may need to repeat in 1 wk)
- CT angiography has high sensitivity and specificity for PE, may also suggest other etiology
- V/Q scan useful when CT angio not available, or patient unable to tolerate IV contrast (e.g. renal failure, allergy)

## Management of DVT/PE

- LMWH unless patient also has renal failure
  - dalteparin 200 IU/kg SC q24h or enoxaparin 1.5 mg/kg SC q24h
- warfarin started at same time as LMWH (5 mg PO OD initially)
- LMWH discontinued when INR has been therapeutic (2-3) for 2 consecutive days
  - early ambulation with analgesia is safe if appropriately anticoagulated
- IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
- consider thrombolysis if extensive DVT or PE causing hemodynamic compromise
  - often can be treated as outpatient, may require analgesia for chest pain (narcotic or NSAID)
- admit if hemodynamically unstable, require supplemental O<sub>2</sub>, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy
  - consider referral to medicine for coagulopathy and malignancy work-up
- long term anticoagulation
  - if reversible risk factor: 3-6 mo of warfarin
  - idiopathic VTE: may need longer term warfarin (5 yr or more)

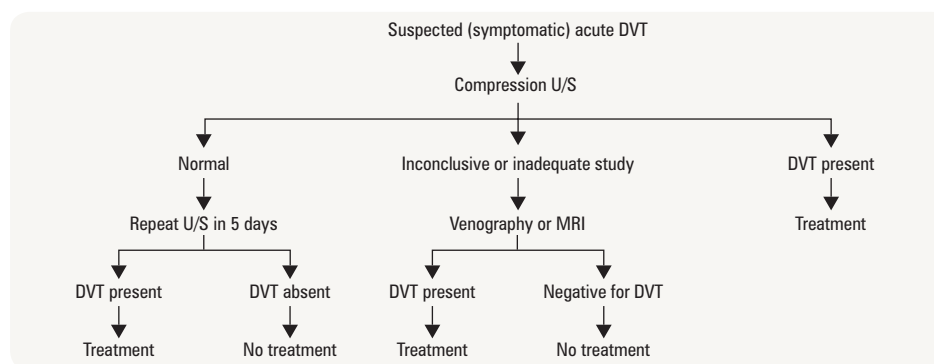


Figure 11. Approach to Suspected DVT

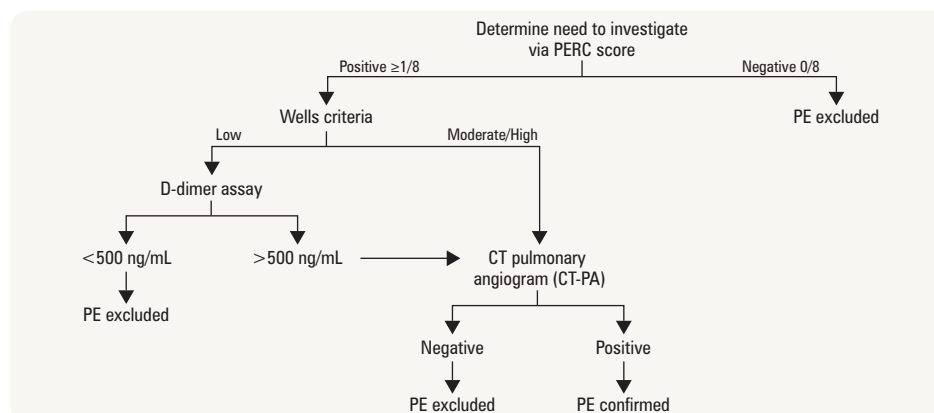


Figure 12. Approach to suspected PE



### PERC Score

- Age >50 yr
- HR >100 bpm
- O<sub>2</sub> sat on RA <94%
- Prior history DVT/PE
- Recent trauma or surgery
- Hemoptysis
- Exogenous estrogen
- Clinical signs suggesting DVT

Score 1 for each question; a score 0/8 means patient has <1.6% chance having a PE and avoids further investigation. It is important to note that this clinical score cannot be applied to pregnant women



### Pre-test Probability for DVT (Wells Score)

Active cancer	+1
Paralysis or immobilization	+1
Recently bedridden >3 d or surgery within 4 wk	+1
Localized tenderness in deep vein system	+1
Entire leg swollen	+1
Calf swelling >3 cm asymptomatic side	+1
Pitting edema on affected side	+1
Superficial (non-varicose) veins	+1
Alternative dx more likely than DVT	-2

0-1: DVT unlikely  
≥2: DVT likely

Adapted from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management *Lancet* 2002;350:1795-1798



### Wells Criteria for PE

Previous Hx of DVT/emboli	+1.5
HR >100	+1.5
Recent immobility or Sx	+1.5
Clinical signs of DVT	+3
Alternate Dx less likely than PE	+3
Hemoptysis	+1
Cancer	+1

0-2: Low probability  
2-6: Intermediate probability  
>6: High probability



D-dimer is only useful if it is negative. Negative predictive value >99%.



50% of patients with symptomatic proximal DVT will develop PE, often within days to weeks of the event.

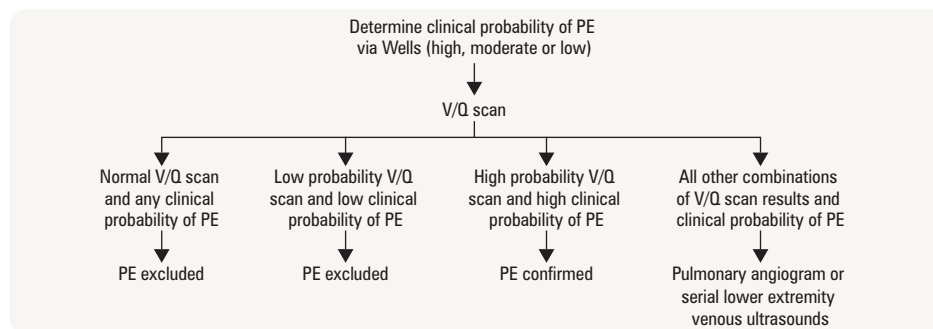


Figure 13. V/Q-based algorithm for suspected PE



#### Clinical Criteria to Prevent Unnecessary Diagnostic Testing in Emergency Department Patients with Suspected Pulmonary Embolism

*J Thromb Haemost* 2004;2:1247-1255

**Purpose:** To develop pulmonary embolism (PE) rule-out criteria (PERC) that can be used at the bedside, and prevents overtesting for PERC. Also, to prevent over-testing for PE, which includes the D-dimer test that frequently results in false positives.

**Study:** 21 variables were collected prospectively from 3148 ER patients evaluated for possible PE to develop rule-out criteria. The application of the developed rules was investigated in 1427 low-risk patients and 382 very low-risk patients.

**Results:** Eight variables were included in a block rule (age <50 yr, pulse <100 bpm, SaO<sub>2</sub> >94%, no unilateral leg swelling, no hemoptysis, no recent trauma or surgery, no prior PE or DVT, no hormone use) and a negative score was used to rule-out PE. In low-risk and very low-risk patients, the rule had a sensitivity of 96 and 100%, respectively and a specificity of 27 and 15%, respectively.

**Summary:** D-dimer testing for PE may not be favourable if all eight factors in the PERC are negative.



#### Precipitating Factors in DKA

##### The 5 Is

Infection  
Ischemia  
Infarction  
Intoxication  
Insulin missed



#### 4 Criteria for DKA Dx

- Hyperglycemia
- Metabolic acidosis
- Hyperketonemia
- Ketonuria



Cerebral edema may occur if hyperosmolality treated too aggressively.

## Diabetic Emergencies

- see also [Endocrinology](#), E11

### Diabetic Ketoacidosis (DKA)

- severe insulin deficiency resulting in hyperglycemia (11-55 mmol/L), dehydration and electrolyte abnormalities
- history and physical examination – often young, type 1 DM, may be first presentation of undiagnosed DM (may occur in small percentage of type 2 patients)
  - early symptoms: polyuria, polydipsia, malaise, nocturia, weight loss
  - late signs and symptoms
    - ♦ anorexia, nausea, vomiting, dyspnea (often due to acidosis), fatigue
    - ♦ abdominal pain
    - ♦ drowsiness, stupor, coma
    - ♦ Kussmaul's respiration
    - ♦ fruity acetone breath
- investigations
  - CBC, glucose, electrolytes, BUN/creatinine, Ca<sup>2+</sup>, Mg<sup>2+</sup>, phosphate, urine glucose and ketones
  - ABG
  - ECG (MI possible precipitant; electrolyte disturbances may predispose to dysrhythmia)
- management
  - rehydration
    - ♦ bolus of NS, then high rate NS infusion (beware of overhydration and cerebral edema, especially in pediatric patients)
    - ♦ beware of a pseudohyponatremia due to hyperglycemia (add 3 Na<sup>+</sup> per 10 glucose over 5.5 mmol/L)
  - potassium
    - ♦ essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial K<sup>+</sup> <5.5 mmol/L)
    - ♦ use cardiac monitoring if potassium levels normal or low
  - insulin
    - ♦ critical, as this is the only way to turn off gluconeogenesis/ketosis
    - ♦ do not give insulin if K<sup>+</sup> <3.3 mmol/L
    - ♦ initial bolus of 5-10 U short-acting/regular insulin (or 0.2 U/kg) IV in adults (controversial – may just start with infusion)
    - ♦ followed by continuous infusion at 5-10 U (or 0.1 U/kg) per hour
    - ♦ add D5W to IV fluids when blood glucose <15 mM to prevent hypoglycemia
  - bicarbonate is not given unless patient is at risk of death or shock (typically pH <7.0)

### Hyperosmolar Hyperglycemic State (HHS)

- state of extreme hyperglycemia (44-133.2 mmol/L) due to relative insulin deficiency, increased counter-regulatory hormones, gluconeogenesis, and dehydration (due to osmotic diuresis) in type 2 DM, high mortality (5-20%)
- history and physical examination
  - mental disturbances, coma, delirium, seizures
  - polyuria
  - nausea, vomiting
- investigations
  - CBC, electrolytes, creatinine, BUN, glucose, Mg<sup>2+</sup>, phosphate, urine glucose and ketones
  - ABG
  - ECG
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O<sub>2</sub> and cardiac monitoring, frequent electrolyte and glucose monitoring
  - insulin as required
  - identify and treat precipitant if present (the 5 Is)

## Hypoglycemia

- very common ED presentation
- management focus
  - treatment of hypoglycemia
  - investigation of cause (most often due to exogenous insulin, alcohol, sulfonylureas)
- history and physical examination
  - last meal, known diabetes, prior similar episodes, drug therapy and compliance
  - liver/renal/endocrine/neoplastic disease
  - depression, alcohol or drug use
- management
  - IV access and rapid blood glucose measurement
  - D50W 50 mL IV push, glucose PO if mental status permits
    - ♦ if IV access not possible, glucagon 1-2 mg IM, repeat x 1 in 10-20 min
  - O<sub>2</sub>, cardiac, frequent BG monitoring
  - thiamine 100 mg IM
  - full meal as soon as mental status permits
  - if episode due to long acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long t<sub>1/2</sub> (may require admission for monitoring)
  - search for cause



### Drugs Inducing Hypoglycemia

Insulin	Sulfa abx
Sulfonylureas	Clotrimazole
Ethanol	Ampicillin
Salicylates	Tetracycline
Acetaminophen	Amphetamines
NSAIDs	Cocaine
β-adrenergic agonists	Pyridoxine
Lithium	ACE-inhibitor
Calcium	Theophylline
MAOI	Quinine
Coumadin	

## Electrolyte Disturbances

- see [Nephrology](#), NP7 and [Endocrinology](#), E38



Table 16. Electrolyte Disturbances

Electrolyte Disturbance	Common Causes	Symptoms	Treatment	Special Considerations
<b>Hypernatremia</b>	Inadequate H <sub>2</sub> O intake (elderly/disabled) or inappropriate excretion of H <sub>2</sub> O (diuretics, Li and DI)	Lethargy, weakness, irritability, and edema. Seizures and coma occur with severe elevations of Na <sup>+</sup> levels (> 158 mmol/L)	Salt restrict and give free water	No more than 12 mmol/L in 24 h drop in Na <sup>+</sup> (0.5 mmol/L/h) due to risk of cerebral edema, seizures, death
<b>Hypонатremia</b>	Hypo-osmolar (dilutional e.g. CHF, cirrhosis, ascites) and hyper-osmolar (usually glucose)	Acute: Neurologic symptoms 2° to cerebral edema, headache, decreased LOC, depressed reflexes	Water restrict Acute: correct rapidly 3% NaCl 1-2 cc/kg/h Chronic: IV NS + furosemide	Limit total rise to 8 mmol/L in 24 h (0.5 mmol/L/h maximum) as patients are at risk of central pontine myelinolysis
<b>Hyperkalemia</b>	Rhabdomyolysis, insulin deficiency, metabolic acidosis	Nausea, palpitations, muscle stiffness, areflexia	Protect heart: Calcium gluconate Shift K <sup>+</sup> into cells: Insulin R, NaHCO <sub>3</sub> , salbutamol	ECG: Peaked/narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, AV block, V fib
<b>Hypokalemia</b>	Metabolic alkalosis, insulin, diuretics, anorexia, salbutamol	Nausea, vomiting, fatigue, muscle cramps, constipation	K-Dur®, K <sup>+</sup> sparing diuretics, IV solutions with 20-40 mEq KCl per liter over 3-4 h	ECG: U waves most important, flattened/ inverted T waves, prolonged QT, depressed ST May need to restore Mg <sup>2+</sup>
<b>Hypercalcemia</b>	Hyper-PTH and malignancy account for approx. 90% of cases	Multisystem including CVS, GI (groans), renal (stones), rheumatological, MSK (bones), psychiatric (moans)	Isotonic saline + furosemide if hypervolemic Bisphosphonates, dialysis, chelation (EDTA or oral phosphate)	Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy
<b>Hypocalcemia</b>	Iatrogenic, low Mg <sup>2+</sup> , liver dysfunction, 1° hypo-PTH	Laryngospasm, hyperreflexia, parasthesia, tetany, Chvostek's and Trousseau's sign	Acute (ionized Ca <sup>2+</sup> <0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion	Prolonged QT interval can arise leading to dysrhythmias as can upper airway obstruction

## Hypertensive Emergencies

### Hypertensive Emergency (Hypertensive Crisis)

#### Etiology

- essential hypertension, emotional exertion, pain, use of sympathomimetic drugs (cocaine, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), pheochromocytoma, pregnancy

#### Presentation

- elevation of systolic and diastolic BP (irrespective of BP) with acute end-organ damage (CNS, renal, CVS, retinal)



**HELLP Syndrome** (seen only in preeclampsia/eclampsia)  
**H**emolytic anemia  
**E**levated Liver enzymes  
**L**ow Platelet count



### Catecholamine Induced Hypertensive Emergencies

Avoid use of non-selective β-blockers as they inhibit β-mediated vasodilation and leave α-adrenergic vasoconstriction unopposed.



**Table 17. Signs and Symptoms of Hypertensive Emergencies**

	Central Nervous System	Retinal	Renal	Cardiac	Gastrointestinal
<b>Complication</b>	Stroke/TIA, headache, altered mental status, seizures, hemorrhage	Vision change, hemorrhage, exudates, papilledema	Nocturia, elevated creatinine, proteinuria, hematuria, oliguria	Ischemia/angina, infarct, dissection (back pain), congestive heart failure	Nausea, vomiting, abdominal pain, elevated liver enzymes

**Investigations**

- CBC, electrolytes, BUN, creatinine, urinalysis
- peripheral blood smear: to detect microangiopathic hemolytic anemia
- CXR: if SOB or chest pain
- ECG, troponins, CK: if chest pain
- CT head: if neurological findings or severe headache
- toxicology screen if sympathomimetic overdose suspected

**Management**

- in general, the strategy for management is to gradually and progressively reduce blood pressure in 24-48 h. Refer to Table 18 for common agents
  - lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually nitroprusside and labetalol) or adjusting antihypertensive
  - if preeclampsia, immediately consult OB/GYN (see [Obstetrics](#), OB16)
  - transfer to ICU for further reduction in BP under monitored setting
- in case of ischemic stroke: do not rapidly reduce blood pressure, maintain BP above 150/100 for 5 d
- in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
- in case of excessive catecholamines: avoid  $\beta$ -blockers (except labetalol)
- in case of acute coronary syndrome: address ischemia initially, then BP

**Hypertensive Urgency**

- definition: severely elevated blood pressure (usually sBP >180, dBP >115) with no evidence of end-organ damage
- most commonly due to non-adherence with medications
- treatment: initiate/adjust antihypertensive therapy, monitor in ED (up to 6 h) and discharge with follow up for 48-72 h
- goal: differentiate hypertensive emergencies from hypertensive urgencies

**Table 18. Most Commonly Used Agents for the Treatment of Hypertensive Crisis**

Drug	Dosage	Onset of Action	Duration of Action	Adverse Effects*	Special Indications
<b>VASODILATORS</b>					
Sodium Nitroprusside (vascular smooth muscle dilator) 1st line	0.25-10 $\mu$ g/kg/min	Immediate	3-5 min	N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome	Most hypertensive emergencies (especially CHF, aortic dissection) Use in combination with $\beta$ -blockers (e.g. esmolol) in aortic dissection Caution with high ICP and azotemia
Nicardipine (CCB)	2 mg IV bolus, then 4 mg/kg/h IV	15-30 min	40 min	Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, RF, eclampsia, sympathetic crisis)	Most hypertensive emergencies Caution with acute CHF
Fenoldopam Mesylate (dopamine receptor antagonist)	0.05-0.1 $\mu$ g/kg/min IV	<5 min	8-10 min	Tachycardia, headache, nausea, flushing (e.g. acute RF)	Most hypertensive emergencies Caution with glaucoma
Enalapril (ACEI)	0.625-1.25 mg IV q6h	15-30 min	12-24 h	Theoretical fall in pressure in high renin states not seen in studies	Acute LV failure Avoid in acute MI, pregnancy, acute RF
Nitroglycerin	5-20 $\mu$ g/min IV	1-2 min	3-5 min	Hypotension, bradycardia, headache, lightheadedness, dizziness	MI/pulmonary edema
Hydralazine	5-10 mg IV/IM q20min (max 20 mg)	5-20 min	2-6 h	Dizziness, drowsiness, headache, tachycardia, $\text{Na}^+$ retention	Eclampsia

**Signs/Symptoms of CNS Hypertensive Emergency**

- Nausea and vomiting
- Seizure
- Headache or altered mental status
- Cushing response



With CNS manifestations of severe hypertension, it is often difficult to differentiate causal relationships [i.e. hypertension could be secondary to primary cerebral event (Cushing effect)].



Most commonly used agents for hypertensive crisis are labetalol and nitroprusside.

**Drugs that Increase Adrenergic Stimulation**

- MAOIs
- TCAs
- Amphetamines
- Cocaine



**Table 18. Most Commonly Used Agents for the Treatment of Hypertensive Crisis** (continued)

Drug	Dosage	Onset of Action	Duration of Action	Adverse Effects*	Special Indications
<b>ADRENERGIC INHIBITORS</b>					
Labetalol	20 mg IV bolus q10min or 0.5-2 mg/min	5-10 min	3-6 h	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies (esp. eclampsia) Avoid in acute CHF; heart block >1st degree
Esmolol	250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat	1-2 min	10-20 min	Hypotension, nausea, bronchospasm	Aortic dissection, acute MI SVT dysrhythmias, perioperative HTN Avoid in acute CHF; heart block >1st degree
Phentolamine	5-15 mg q5-15min	1-2 min	3-10 min	Tachycardia, headache, flushing	Catecholamine excess (e.g. pheochromocytoma)

\*Hypotension may occur with all of these agents

## Stroke

- see [Neurology](#), N43
- can be ischemic (80% of all strokes) or hemorrhagic

### Presentation

- sudden onset persisting neurological deficits

**Table 19. Signs and Symptoms of Stroke**

	General	Language/throat	Vision	Cordination	Motor	Sensation	Reflex
<b>Sign/symptoms</b>	Decreased LOC, changed mental status, confusion, neglect	Dysarthria, aphasia, swallowing difficulty	Diplopia, eye deviation, asymmetric pupils, visual field defect	Ataxia, intention tremor, lack of coordination	Increased tone, loss of power, spasticity	Loss of sensation	Hyper reflexia, clonus

Note: headache is variable

- patients with hemorrhagic stroke can present with sudden onset thunderclap headache that is usually described as “worst headache in my life”
- constellation of neurological deficits can point to certain vascular territories (Table 20)
- stroke mimics: seizure, migraine, hypoglycemia, Todds paralysis, peripheral nerve injury, Bell's palsy, tumour, syncope

**Table 20. Stroke Syndromes**

Region of Stroke	Stroke Syndrome
Anterior Cerebral Artery	Primarily frontal lobe function affected  Altered mental status, impaired judgment, contralateral lower extremity weakness and hypoesthesia, gait apraxia
Middle Cerebral Artery	Contralateral hemiparesis (arm and face weakness > leg weakness) and hypoesthesia, ipsilateral hemianopsia, gaze preference to side of lesion ± agnosia, receptive/expressive aphasia
Posterior Cerebral Artery	Affects vision and thought  Homonymous hemianopsia, cortical blindness, visual agnosia, altered mental status, impaired memory
Vertebrobasilar Artery	Wide variety of CN, cerebellar and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypoesthesia, syncope, ataxia Loss of pain and temperature sensation ipsilateral face and contralateral body

### Investigations

- CBC, electrolytes, blood glucose, coagulation studies, ± cardiac biomarkers, ± toxicology screen
- non-contrast CT head: look for hemorrhage, ischemia
- ECG ± echocardiogram: rule out atrial fibrillation, acute MI as source of emboli
  - other imaging: carotid dopplers, CTA, MRA as appropriate



If patient presents within 4.5 h of onset of disabling neurological deficits greater than 60 min with no signs of resolution, they may be a candidate for thrombolysis. Do brief assessment and order stat CT head.

#### Exclusion Criteria for tPA:

- Suspected subarachnoid hemorrhage
- Previous intracranial hemorrhage
- Cerebral infarct or severe head injury within the past 3 mo
- Recent pericarditis
- Major surgery within the past 14 d
- GI or urinary hemorrhage within the past 21 d
- Recent lumbar puncture or arterial puncture at noncompressible site
- Patient is pregnant
- BP >185 mmHg systolic, or >110 mmHg diastolic
- Bleeding diathesis
- Prolonged PTT (more than 40 s) or INR >1.4
- Platelet count <100,000
- Blood glucose <2.8 or >22 mmol/L
- Intracranial hemorrhage on CT or large volume infarct
- Seizure at onset causing deficit
- Previously ADL dependent (clinical judgment)



#### Differentiation of UMN Disease versus LMN Disease

Category	UMN Disease	LMN Disease
Muscular deficit	Muscle groups	Individual muscles
Reflexes	Increased	Decreased/absent
Tone	Increased	Decreased
Fasciculations	Absent	Present
Atrophy	Absent/minimal	Present
Babinski	Upgoing	Downgoing

## Management

- thrombolysis: immediate assessment for eligibility. Need acute onset, <4.5 h from drug administration time AND compatible physical findings AND normal CT with no bleed
- intubation with RSI if GCS  $\leq 8$ , rapidly decreasing GCS, or inadequate airway protection reflexes
- elevating head of bed if risk of elevated ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV  $\pm$  cardiac monitoring
  - judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischemic penumbra)
- BP control: only treat severe hypertension (sBP >200, dBP >120, mean arterial BP >140) or hypertension associated with hemorrhagic stroke transformation, cardiac ischemia, aortic dissection, or renal damage; use IV nitroprusside or labetalol
- glycemic control: keep fasting glucose less than 6.5 in acute phase (5 d)
- cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- consult neurosurgery, neurology, medicine as indicated

## Medications

- acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 4.5 h of symptom onset with no evidence of hemorrhage on CT scan
- antiplatelet agents: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin<sup>®</sup> (1<sup>st</sup>-line); clopidogrel, Aggrenox<sup>®</sup> (2<sup>nd</sup>-line)
- anticoagulation: DVT prophylaxis if immobile; treat atrial fibrillation if present



### 7 Causes of Emboli from the Heart

- Atrial fibrillation
- MI
- Endocarditis
- Valvular disease
- Dilated cardiomyopathy
- Left heart myxoma
- Prosthetic valves



### Causes of Acute Ataxia

#### UNABLE TO STAND

Underlying weakness (mimic ataxia)  
Nutritional neuropathy (vitamin B<sub>12</sub> deficiency)

Arteritis/vasculitis

Basilar migraine

Labyrinthitis/vestibular neuronitis

Encephalitis/infection

Trauma (post-concussive)

Other (rare genetic or metabolic disease)

Stroke (ischemia or hemorrhage)

Toxins (drugs, toluene, mercury)

Alcohol

Neoplasm/paraneoplastic syndrome

Demyelination (Miller Fisher, Guillain Barré, MS)



Vaginal bleeding can be life threatening. Always start with ABCs and ensure your patient is stable.



Need  $\beta$ -hCG  $\geq 1200$  to see intrauterine changes on transvaginal U/S.



An ectopic pregnancy can be ruled out by confirming an intrauterine pregnancy by bedside U/S unless the patient is using IVF.

# Gynecologic/Urologic Emergencies

## Vaginal Bleed

- see [Gynecology](#), GY6 and [Obstetrics](#), OB22

## Etiology

- pregnant patient
  - 1st/2<sup>nd</sup> trimester pregnancy: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause)
  - 2<sup>nd</sup>/3<sup>rd</sup> trimester pregnancy: placenta previa, placental abruption, premature rupture of membranes, preterm labour
  - other: trauma, bleeding cervical polyp
- postpartum
  - postpartum hemorrhage, uterine inversion, retained placental tissue, endometritis
- non-pregnant patients
  - dysfunctional uterine bleeding, uterine fibroids, pelvic tumours, trauma, endometriosis, PID, exogenous hormones

## History

- characterize bleeding (frequency, duration, number of pads/tampons, cyclicity)
- pain (if present OPQRSTU)
- menstrual history, sexual history, STI history, syncope/pre-syncope
- details of pregnancy including gush of fluid and fetal movement (>20 wk)

## Physical Examination

- ABC (especially noting postural BP/HR and mucous membrane)
- abdominal examination (peritoneal signs, tenderness, distention, mass)
- speculum examination (NOT IF 2<sup>nd</sup>/3<sup>rd</sup> trimester bleeding. Perform only when placenta previa is ruled out with ultrasound)
  - look for active bleeding, trauma/anomaly, and cervical dilatation
  - use sterile speculum if pregnant
- bimanual examination (cervical tenderness, size of uterus, cervical length/dilatation)
  - sterile gloves if pregnant

## Investigations

- $\beta$ -hCG test for all patients with child-bearing potential
- CBC, blood and Rh type, quantitative  $\beta$ -hCG, PTT, INR
- type and cross if significant blood loss
- transvaginal ultrasound (rule out ectopic pregnancy and spontaneous abortion)
- abdominal ultrasound (rule out placenta previa and fetal demise)
- postpartum
  - U/S for retained products
  - $\beta$ -hCG if concerned about retained tissue

## Management

- ABCs
- pulse oximeter and cardiac monitors if unstable
- Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
- 1<sup>st</sup>/2<sup>nd</sup> trimester pregnancy
  - ectopic pregnancy: definitive treatment with surgery or methotrexate
  - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
  - U/S indeterminate or  $\beta$ -hCG >1000-2000 IU: further work-up and/or gynecology consult
  - abortions: if complete, discharge if stable; for all others, acquire gynecology consult
- 2<sup>nd</sup>/3<sup>rd</sup> trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type and cross 4 units of blood, consult OB/GYN immediately
- non-pregnant
  - dysfunctional uterine bleeding (prolonged or heavy flow  $\pm$  breakthrough bleeding and without ovulation, a diagnosis of exclusion)
    - ♦ <35-40 yr of age: Provera® 10 mg PO OD x 10 d, warn patient of a withdrawal bleed, discharge if stable
    - ♦ if unstable, admit for IV hormonal therapy, possible D&C
    - ♦ >35-40 yr of age: uterine sampling necessary prior to initiation of hormonal treatment to rule out endometrial cancer, U/S for any masses felt on exam
    - ♦ tranexamic acid (Cyklokapron®) to stabilize clots
  - structural abnormalities: fibroids or uterine tumours may require excision for diagnosis/treatment, U/S for workup of other pelvic masses, Pap smear/biopsy for cervical lesions

## Disposition

- the decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult gynecology for admitted patients
- if patient can be safely discharged, ensure follow up with family physician or gynecologist
  - instruct patient to return to emergency for increased bleeding, presyncope



### Classifying Miscarriage (abortion):

**Missed:** non-viable intrauterine pregnancy

**Threatened:** viable intrauterine pregnancy with os closed

**Inevitable:** os closed, no products of conception passed

**Incomplete:** products of conception partially expelled

**Complete:** products of conception completely expelled

**Septic:** any of above with presence of infection (usually incomplete)

**Recurrent:** >3 spontaneous abortions (recurrent pregnancy loss)



Vaginal bleeding (and its underlying causes) can be a very distressing event for patients.

Ensure appropriate support is provided.

## Pregnant Patient in the ER

Table 21. Complications of Pregnancy

Trimester	Fetal	Maternal
First 1-12 wk	Pregnancy failure <ul style="list-style-type: none"> <li>• Spontaneous abortion</li> <li>• Fetal demise</li> <li>• Gestational trophoblastic disease</li> </ul>	Ectopic pregnancy Anemia Hyperemesis gravidarum UTI/pyelonephritis
Second 13-27 wk	Disorders of fetal growth <ul style="list-style-type: none"> <li>• IUGR</li> <li>• Oligo/polyhydramnios</li> </ul>	Gestational diabetes mellitus Rh incompatibility UTI/pyelonephritis
Third 28-41 wk	Vasa previa	Preterm labour/PPROM Preeclampsia/eclampsia Placenta previa Placental abruption Uterine rupture DVT

## Nephrolithiasis (Renal Colic)

- see [Urology](#), U16

### Epidemiology and Risk Factors

- 10% of population (twice as common in males)
- recurrence 50% at 5 yr
- peak incidence 30-50 yr of age
- 75% of stones <5 mm pass spontaneously within 2 wk, larger stones may require consultation

### Clinical Features

- urinary obstruction  $\rightarrow$  upstream distention of ureter or collecting system  $\rightarrow$  severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis
- peritoneal findings/anterior abdominal tenderness usually absent



### Kidney Stones

- 80% Calcium
- 10% Struvite
- 10% Uric acid

### Differential Diagnosis of Renal Colic

- acute ureteric obstruction
- acute abdomen: biliary, bowel, pancreas, AAA
- gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1): herpes zoster, nerve root compression

### Investigations

- screening
  - CBC → elevated WBC in presence of fever suggests infection
  - electrolytes, Cr, BUN → to assess renal function
  - urinalysis: R&M (WBCs, RBCs, crystals), C&S
- imaging
  - non-contrast spiral CT is the study of choice
  - abdominal ultrasound may demonstrate stone or hydronephrosis (consider in females of child bearing age)
  - abdominal x-ray will identify large radiopaque stones (calcium, struvite, and cystine stones) but may miss smaller stones, uric acid stones or stones overlying bony structures. Consider as an initial investigation in patients who have a history of radiopaque stones and similar episodes of acute flank pain (CT necessary if film is negative)
- strain all urine → stone analysis

### Management

- analgesics: NSAIDs [usually ketorolac (Toradol®) preferable over opioids], antiemetics, IV fluids
- urology consult may be indicated, especially if stone >5 mm, or if patient has signs of obstruction or infection
- α-blocker (e.g. tamsulosin) helpful to increase stone passage in select cases

### Disposition

- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and is able to tolerate oral medications
- may advise hydration, and limitation of protein, sodium, oxalate and alcohol intake



#### Indications for Admission to Hospital

- Intractable pain
- Fever (suggests infection) or other evidence of pyelonephritis
- Single kidney with ureteral obstruction
- Bilateral obstructing stones
- Intractable vomiting
- Compromised renal function



ALWAYS assess visual acuity in both eyes when a patient presents to the ER with an ophthalmologic complaint.



Any etiology of red eyes may also present with blurred vision.



#### Other Ophthalmologic Emergencies (See also [Ophthalmology](#), OP5)

**Infectious:** Red eye (Table 22), endophthalmitis, hypopyon.

**Trauma:** Globe rupture, orbital blow-out fractures, corneal injuries, eyelid laceration, hyphema, lens dislocation, retrolental hemorrhage.

**Painful vision loss:** Acute iritis, corneal abrasion, globe rupture, lens dislocation, retrolental hemorrhage, optic neuritis, temporal arteritis, endophthalmitis, keratitis.

**Painless vision loss:** Central retinal vein occlusion, amaurosis fugax, occipital stroke.



#### Contraindications to Pupil Dilation

- Shallow anterior chamber
- Iris-supported lens implant
- Potential neurological abnormality requiring pupillary evaluation
- Caution with CV disease – mydriatics can cause tachycardia

## Ophthalmologic Emergencies

- see also [Ophthalmology](#), OP17



### History/Physical

- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital x-rays, ultrasound, or CT scan to exclude presence of intraocular metallic foreign body
- see Table 22 for important considerations of red eye in the emergency department
- visual acuity in both eyes, pupils, extraocular structures, fundoscopy, tonometry, slit lamp exam

### Management of Ophthalmologic Foreign Body

- copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab or sterile needle
- antibiotic drops qid until healed
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only
- consider tetanus prophylaxis
- ophthalmology consult if globe penetration suspected

**Table 22. Differential Diagnosis of Red Eye in the Emergency Department**

Symptom	Possible Serious Etiology
Light sensitivity	Iritis, keratitis, abrasion, ulcer
Unilateral	Above + herpes simplex, acute angle closure glaucoma
Significant pain	Above + scleritis
White spot on cornea	Corneal ulcer
Blurred vision	All of the above
Non-reactive pupil	Acute glaucoma, iritis
Copious discharge	Gonococcal conjunctivitis
Blurred vision	All of the above

**Table 23. Select Ophthalmologic Emergencies**

Condition	Signs and Symptoms	Management
<b>Acute angle closure glaucoma</b>	Unilateral red, painful eye Decreased visual acuity, halos around lights Fixed, mid-dilated pupil Nausea, vomiting Marked increase in IOP (>40 mmHg) Shallow anterior chamber $\pm$ cells	Ophthalmology consult for laser iridotomy Topical $\beta$ -blockers, adrenergics and cholinergics Systemic carbonic anhydrase inhibitors and hyperosmotic agents
<b>Chemical burn</b>	Known exposure to acids or alkali (worse) Pain, decreased visual acuity Vascularization or defects of cornea Iris and lens damage	Irrigate at site of accident IV NS drip in ED with eyelid retracted Swab fornices Cycloplegic drops Topical antibiotics and patching
<b>Orbital cellulitis</b>	Red, painful eye, decreased visual acuity Headache, fever Lid erythema, edema and difficulty opening eye Conjunctival injection and chemosis Proptosis, ophthalmoplegia $\pm$ RAPD	Admission, ophthalmology consult Blood cultures, orbital CT IV antibiotics (ceftriaxone+ vancomycin) Drainage of abscess
<b>Retinal artery occlusion</b>	Sudden, painless, monocular vision loss RAPD Cherry red spot and retinal pallor on fundoscopy	Restore blood flow <2 h Massage globe Decreased IOP (topical $\beta$ -blockers, inhaled $O_2/CO_2$ mix, IV Diamox <sup>®</sup> , IV mannitol, drain aqueous fluid)
<b>Retinal artery detachment</b>	Flashes of light, floaters, curtains of blackness/ peripheral vision loss Painless Loss of red reflex, decreased IOP Detached areas are grey $\pm$ RAPD	Ophthalmology consult for scleral buckle/ pneumatic retinoplexy

## Dermatologic Emergencies

### Life Threatening Dermatoses

#### Rash Characteristics

##### A. Diffuse Rashes

- staphylococcal scalded skin syndrome (SSSS)
  - ♦ caused by an exotoxin from infecting strain of coagulase-positive *S. aureus*
  - ♦ mostly occurs in children
  - ♦ prodrome: fever, irritability, malaise and skin tenderness
  - ♦ sudden onset of diffuse erythema: skin is red, warm, and very tender
  - ♦ flaccid bullae that are difficult to see, then desquamate in large sheets
  - ♦ Nikolsky's sign: gentle lateral stroking of skin causes epidermis to separate
- toxic epidermal necrolysis (TEN) [ $>30\%$  of Body SA]
  - ♦ see also [Dermatology](#), D22
  - ♦ caused by drugs (e.g. phenytoin, sulfas, penicillins and NSAIDs), bone marrow transplantation, blood product transfusions
  - ♦ usually occurs in adults
  - ♦ diffuse erythema followed by necrosis
  - ♦ severe mucous membrane blistering
  - ♦ entire epidermis desquamation
  - ♦ high mortality ( $>50\%$ )
- toxic shock syndrome (TSS)
  - ♦ see also [Infectious Diseases](#), ID26
  - ♦ caused by superantigen from *S. aureus* or GAS activating T-cell and cytokines
  - ♦ patient often presents with onset of shock and multi-organ failure, fever
  - ♦ diffuse erythematous macular rash
  - ♦ at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, skin (necrotizing fasciitis, gangrene)
- vesicobullous lesions
  - erythema multiforme (EM)
    - ♦ see [Dermatology](#), D22
    - ♦ immunologic reaction to herpes simplex
    - ♦ viral prodrome 1-14 d before rash
    - ♦ "target lesion": central grey bulla or wheal surrounded by concentric rings of erythema and normal skin



- Stevens-Johnson syndrome (SJS) [ $<10\%$  of Body SA]
  - ♦ see also [Dermatology](#), D22
  - ♦ related to drugs such as antiepileptics and biologic agents, e.g. infliximab
  - ♦ EM with constitutional symptoms and mucous membrane involvement (milder mucous membrane involvement than TEN)



## B. Discrete Lesions

- pyoderma gangrenosum
  - ♦ often associated with immunocompromised patients (HIV, leukemia or lymphoma) with Gram-negative sepsis
  - ♦ often occurs in arms, hands, feet, or perineal region
  - ♦ usually begins as painless macule/vesicle  $\rightarrow$  pustule/bulla on red/blue base  $\rightarrow$  sloughing, leaving a gangrenous ulcer
- disseminated gonococcal infection (DGI)
  - ♦ see also [Dermatology](#), D32
  - ♦ fever, skin lesions (pustules/vesicles on erythematous base  $\sim 5$  mm in diameter), arthritis (joint swelling and tenderness), septic arthritis (in larger joints, e.g. knees, ankles and elbows)
  - ♦ most commonly in gonococcus positive women during menstruation or pregnancy
  - ♦ skin lesions usually appear in extremities and resolve quickly ( $<7$  d)
- meningococcemia
  - ♦ flu-like symptoms of headache, myalgia, nausea and vomiting
  - ♦ petechial, macular or maculopapular lesions with grey vesicular centres
  - ♦ usually a few millimeters in size but may become confluent and hemorrhagic
  - ♦ usually appear in extremities but may appear anywhere
  - ♦ look for signs of meningeal irritation: Brudzinski, Kernig, nuchal rigidity, jolt accentuation



## History and Physical Examination

- determine onset, course, location of skin lesions
- fever, joint pain
- associated symptoms: CNS, resp, GU, GI, renal, liver, mucous membranes
- medication history
- vitals

## Investigations

- immediate consultation if patient unstable
- CBC, electrolytes, creatinine, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)

## Management

- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevention of infection
- determine if admission and consult needed: dermatology or infectious diseases
- specific management is determined by etiology
  - SSSS, TSS, DGI and meningococcemia
    - ♦ IV antibiotics
  - EM, SJS, and TEN
    - ♦ stop precipitating medication
    - ♦ fluids
    - ♦ symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IVIG
    - ♦ TEN: debride necrotic tissue

## Disposition

- most cases will require urgent care and hospitalization
- TEN: early transfer to burn centre improves outcome



Thorough dermatologic examinations are required; examination of asymptomatic skin may identify more lesions! Ensure adequate draping during dermatologic examinations.

# Environmental Injuries



## Heat Exhaustion and Heat Stroke

- predisposing factors: young persons who overexert themselves, older adults who cannot dissipate heat at rest (e.g. using anticholinergic drugs such as antihistamines or TCAs), and patients with schizophrenia who are using anticholinergic or neuroleptic medications

### Heat Exhaustion (HE)

- clinical features relate to loss of circulating volume caused by exposure to heat stress
- “water depletion”: HE occurs if lost fluid not adequately replaced
- “salt depletion”: HE occurs when losses replaced with hypotonic fluid



Heat exhaustion (HE) may closely resemble heat stroke. HE may eventually progress to heat stroke, therefore, if diagnosis is uncertain treat as heat stroke.



## Heat Stroke

- life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
- divided into classical and exertional subtypes (see Table 24)
- if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, other infections)

**Table 24. Heat Exhaustion vs. Heat Stroke**

	Heat Exhaustion	Classical Heat Stroke	Exertional Heat Stroke
<b>Clinical Features</b>	<ul style="list-style-type: none"> <li>• Non-specific malaise, headache, fatigue</li> <li>• Body temp <math>&lt;40.5^{\circ}\text{C}</math> (usually normal)</li> <li>• No coma or seizures</li> <li>• Dehydration (<math>\uparrow</math> HR, orthostatic hypotension)</li> </ul>	<ul style="list-style-type: none"> <li>• Occurs in setting of high ambient temperatures (e.g. heat wave, poor ventilation)</li> <li>• Often patients are older, poor, and sedentary or immobile</li> <li>• Dry, hot skin</li> <li>• Temp usually <math>&gt;40.5^{\circ}\text{C}</math></li> <li>• Altered mental status, seizures, delirium, coma</li> <li>• May have elevated AST, ALT</li> </ul>	<ul style="list-style-type: none"> <li>• Occurs with high endogenous heat production (e.g. exercise) and overwhelmed homeostatic mechanisms</li> <li>• Patients often younger, more active</li> <li>• Skin often diaphoretic</li> <li>• Other features as for classical HS, but may also have DIC, acute renal failure, rhabdomyolysis, marked lactic acidosis</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>• Rest in a cool environment</li> <li>• Normal saline IV if orthostatic hypotension; otherwise replace losses slowly PO</li> </ul>	<ul style="list-style-type: none"> <li>• Cool body temperature with water mist (e.g. spray bottle) and standing fans</li> <li>• Ice water immersion also effective; monitor body temp closely to avoid hypothermic overshoot</li> <li>• Secure airway because of seizure and aspiration risk</li> <li>• Give fluid resuscitation if still hypotensive after above therapy</li> <li>• Avoid <math>\alpha</math>-agonists (e.g. epinephrine) peripheral vasoconstriction and antipyretics (e.g. ASA)</li> </ul>	

## Hypothermia and Cold Injuries



### HYPOTHERMIA

- predisposing factors: extremes of age, lack of housing, drug overdose, EtOH ingestion, trauma (incapacitating), cold water immersion, outdoor sports
- treatment based on: (a) re-warming (b) supporting cardiorespiratory function
- complications: coagulopathy, acidosis, ventricular dysrhythmias (VFib), asystole, volume and electrolyte depletion
- labs: CBC, electrolytes, ABG, serum glucose, creatinine/BUN,  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ , amylase, coagulation profile
- imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- monitors: ECG, rectal thermometer, Foley catheter, NG tube, monitor metabolic status frequently

**Table 25. Classification of Hypothermia**

Class	Temp	Symptoms/Signs
<b>Mild</b>	$32\text{--}34.9^{\circ}\text{C}$	Tachypnea, tachycardia, ataxia, dysarthria, shivering
<b>Moderate</b>	$28\text{--}31.9^{\circ}\text{C}$	Loss of shivering, dysrhythmias, Osborne (J) waves on ECG, decreased LOC, combative behaviour, muscle rigidity, dilated pupils
<b>Severe</b>	$<28^{\circ}\text{C}$	Coma, hypotension, acidemia, ventricular fibrillation, asystole, flaccidity, apnea

### Re-warming Options

- gentle fluid and electrolyte replacement in all (due to cold diuresis)
- Passive External Re-warming (PER)
  - suitable for most stable patients with core temperature  $>32.2^{\circ}\text{C}$
  - involves covering patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
- Active External Re-warming (AER)
  - involves use of warming blankets
  - beware of “afterdrop” phenomenon
  - safer when done in conjunction with active core re-warming
- Active Core Re-warming (ACR)
  - generally for patients with core temperature  $<32.2^{\circ}\text{C}$ , and/or with cardiovascular instability
  - avoids “afterdrop” seen with AER alone
  - re-warm core by using
    - ♦ warmed humidified oxygen, IV fluids
    - ♦ peritoneal dialysis with warm fluids
    - ♦ gastric/colonic/pleural irrigation with warm fluids
    - ♦ external circulation (cardiopulmonary bypass machine) is most effective, fastest



#### Afterdrop Phenomenon

Warming of extremities causes vasodilation and movement of cool pooled blood from extremities to core, resulting in a drop in core temperature  $\rightarrow$  cardiac arrest.

### Approach to Cardiac Arrest in the Hypothermic Patient

- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 min; may have profound bradycardia
- **if any pulse at all (even very slow) do NOT do CPR**
- if in VFib try to defibrillate up to maximum 3 shocks if core temperature  $<30^{\circ}\text{C}$
- intubate if required, ventilate with warmed, humidified  $\text{O}_2$
- medications (vasopressors, antidysrhythmics) may not be effective at low temperatures
  - controversial; may try one dose
- focus of treatment is re-warming

### FROSTBITE

#### Classification

- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
- 1st degree
  - symptoms: initial paresthesia, pruritus
  - signs: erythema, edema, hyperemia, no blisters
- 2nd degree
  - symptoms: numbness
  - signs: blistering (clear), erythema, edema
- 3rd degree
  - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
  - signs: hemorrhagic blisters, skin necrosis, edema, no movement

#### Management

- treat for hypothermia:  $\text{O}_2$ , IV fluids, maintenance of body warmth
- remove wet and constrictive clothing
- immerse in  $40\text{--}42^{\circ}\text{C}$  agitated water for 10-30 min (very painful; administer adequate analgesia)
- clean injured area, leave injured region open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin
- tetanus prophylaxis
- consider penicillin G as frost bite injury at high risk of infection
- surgical intervention may be required to release restrictive eschars
- never allow a thawed area to re-chill/freeze



#### Burn Causes

- Thermal (flame, scald)
- Chemical
- Radiation (UV, medical/therapeutic)
- Electrical



Use palm of the patient's hand to estimate 1% of BSA affected.

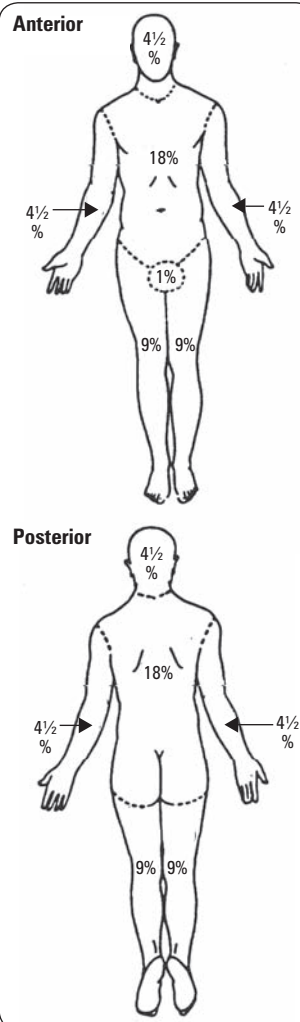


Figure 14. Rule of 9s for total body surface area (BSA)



Intubate early if you suspect inhalation injury, as airway can become obstructed due to edema.

## Burns

- see [Plastic Surgery](#), PL16



#### Physical Examination

- burn size
  - rule of nines (see Figure 14); does not include 1st degree burns
- burn depth
  - superficial: epidermis only (e.g. sunburn)
  - partial thickness: into superficial dermis deep or hair follicles, sweat glands
  - full thickness: all layers of the skin
  - deep: involvement of fat, muscle, even bone

#### Management

- remove noxious agent/stop burning process
- establish airway if needed (indicated with burns  $>40\%$  BSA or smoke inhalation injury)
- resuscitation for 2<sup>nd</sup> and 3<sup>rd</sup> degree burns (after initiation of 2 large bore IVs)
- fluid boluses if unstable
  - Parkland Formula: Ringer's lactate 4 cc/kg/%BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
  - urine output is best measure of resuscitation, should be 40-50 cc/h or 0.5 cc/kg/h; avoid diuretics
- pain relief: continuous morphine infusion with breakthrough bolus
- investigations: CBC, electrolytes, urinalysis, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, systemic antibiotics infrequently indicated
- tetanus prophylaxis if burn is deeper than superficial dermis

#### Disposition

- admit
  - 2<sup>nd</sup> degree burns  $>10\%$  BSA; any significant 3<sup>rd</sup> degree burns
  - 2<sup>nd</sup> degree on face, hands, feet, perineum or across major joints
  - electrical, chemical burns and inhalation injury
  - burn victims with underlying medical problems or immunosuppressed patients

## Inhalation Injury

### Etiology

- carbon monoxide (CO), cyanide (CN) poisoning
- direct thermal injury: limited to upper airway
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

### History and Physical

- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin (unreliable, usually post-mortem finding)
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO<sub>2</sub> normal but O<sub>2</sub> saturation low suggests CO poisoning

### Investigations

- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± bronchoscopy

### Management

- CO poisoning: 100% O<sub>2</sub> ± hyperbaric O<sub>2</sub> (controversial)
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators

## Bites

### MAMMALIAN BITES

- see [Plastic Surgery](#), PL10

### History

- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, rabies risks, HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, “fight bites”

### Physical Examination

- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status

### Investigations

- if bony injury or infection suspected check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds, ± CT to rule out cranial perforation

### Initial Management

- wound cleansing and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
- culture wound if signs of infection (erythema, necrosis or pus); obtain anaerobic cultures if wound foul smelling, necrotizing, or abscess; notify lab that sample is from bite wound

### Prophylactic Antibiotics

- types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
- a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present (efficacy not proven)
- dog and cat bites (pathogens: *Pasteurella multocida*, *S. aureus*, *S. viridans*)
  - 80% of cat bites, 5% of dog bites become infected
  - 1st line: amoxicillin + clavulanic acid
- human bites (pathogens: *Eikenella corrodens*, *S. aureus*, *S. viridans*, oral anaerobes)
  - 1st line: amoxicillin + clavulanic acid
- rabies (see [Infectious Diseases](#), ID21)
  - reservoirs: warm-blooded animals except rodents, lagomorphs (e.g. rabbits)
  - post-exposure vaccine is effective; treatment depends on local prevalence
- suturing
  - vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  - allow avascular structures (i.e. pretibial regions, hands and feet) to heal by secondary intention
  - tetanus immunization if >10 yr or incomplete primary series



#### High Risk Criteria for Infection

##### Wound Factors

- Puncture wounds
- Crush injuries
- Wounds > 12 h old
- Hand or foot wounds
- Wounds near joints

##### Patient Factors

- Immunocompromised
- Age > 50 yr
- Prosthetic joints or valves



#### Consider Admission if:

- Moderate to severe infections
- Infections in immunocompromised patients
- Not responding to oral Rx
- Penetrating injuries to tendons, joints, CNS
- Open fractures



**SNAKE BITES**

- history, physical exam, investigations and initial management similar to mammalian bites
- additional management issues
  - snake bites are rarely fatal but proper precautions must be taken
  - supportive management, observe for compartment syndrome, analgesia, tetanus prophylaxis
  - contact Provincial Poison Information Centre for consultation
  - for the Massasauga Rattle Snake ONLY: if no signs of local tissue damage AND an INR is normal at 6 h after the bite, the patient may be discharged
  - there is NO evidence that constriction bands are helpful AND can be harmful
- if envenomation present, administer antivenom as directed by local Poison Information Centre

**INSECT BITES**

- bee stings
  - 5 types of reactions to stings (local, large local, systemic, toxic, unusual)
  - history and physical exam key to diagnosis; no lab test will confirm
  - investigations: CBC, electrolytes, BUN, creatinine, glucose, ABGs, ECG
  - ABC management, epinephrine 0.1 mg IV over 5 min if shock, antihistamines, cimetidine 300 mg IV/IM/PO, steroids,  $\beta$ -agonists for SOB/wheezing 3 mg in 5 mL NS via nebulizer, local site management
- West Nile virus (see [Infectious Diseases](#), ID27)



## Near Drowning

- most common in children <4 yr and teenagers
- causes lung damage, hypoxemia and may lead to hypoxic encephalopathy
- must also assess for shock, C-spine injuries, hypothermia, scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

**Physical Examination**

- ABCs, vitals: watch closely for hypotension
- lungs: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVS: murmurs, dysrhythmias, JVP (CHF, pneumothorax)
- H&N: assess for C-spine injuries
- neuro: GCS or AVPU, pupils, focal deficits

**Investigations**

- labs: CBC, electrolytes, ABGs, Cr, BUN, urinalysis
- imaging: CXR (pulmonary edema, pneumothorax)
- ECG

**Management**

- ABCs, treat for trauma, shock, hypothermia
- cardiac and O<sub>2</sub> sat monitors, IV access
- intensive respiratory care
  - ventilator assistance if decreased respirations, pCO<sub>2</sub> >50 mmHg, or pO<sub>2</sub> <60 mmHg on maximum O<sub>2</sub>
  - may require intubation for airway protection, ventilation, pulmonary toilet
  - high flow O<sub>2</sub>/CPAP/BiPAP may be adequate but some may need mechanical ventilation with PEEP
- dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, acidosis
- vomiting: very common, NG suction to avoid aspiration
- convulsions: usually respond to O<sub>2</sub>; if not, diazepam 5-10 mg IV slowly
- bronchospasm: bronchodilators
- bacterial pneumonia: not necessary to prophylax with antibiotics unless contaminated water or hot-tub (*Pseudomonas*)
- must observe for at least 24 h as non-cardiogenic pulmonary edema may develop late

**Disposition**

- non-significant submersion: discharge after short observation
- significant submersion (even if asymptomatic): long period of observation (24 h) as pulmonary edema may appear late
- CNS symptoms or hypoxemia: admit
- severe hypoxemia, decreased LOC: ICU

# Toxicology



## Alcohol Related Emergencies

- see also [Psychiatry](#), PS22

### Acute Intoxication

- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia → may progress to coma
- hypotension (peripheral vasodilation)
- if obtunded rule out
  - head trauma/intracranial hemorrhage
  - associated depressants/street drugs, toxic alcohols
    - ♦ may also contribute to respiratory/cardiac depression
  - hypoglycemia (screen with bedside glucometer)
  - hepatic encephalopathy: confusion, altered LOC, coma
    - ♦ precipitating factors: GI bleed, infection, sedation, electrolyte abnormalities, protein meal
  - Wernicke's encephalopathy (ataxia, ophthalmoplegia, delirium)
  - post-ictal state, basilar stroke

### Withdrawal

- beware of withdrawal signs (see Table 26)
- treatment:
  - diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1hr until calm
    - ♦ frequency of dosing may have to be increased depending on clinical response
  - may use CIWA protocol and give benzodiazepines as above until CIWA <10
  - thiamine 100 mg IM/IV then 50-100 mg/d
  - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  - admit patients with delirium tremens (DT), or multiple seizures

**Table 26. Alcohol Withdrawal Signs**

Time Since Last Drink	Syndrome	Description
6-8 h	Mild withdrawal	Generalized tremor, anxiety, agitation, but no delirium Autonomic hyperactivity (sinus tachycardia), insomnia, nausea, vomiting
1-2 d	Alcoholic hallucinations	Visual (most common), auditory and tactile hallucinations Vitals often normal
8 h-2 d	Withdrawal seizures	Typically brief generalized tonic-clonic seizures May have several within a few hours CT head if focal seizures have occurred
3-5 d	Delirium tremens (DT)	5% of untreated withdrawal patients Severely confused state, fluctuating levels of consciousness Agitation, insomnia, hallucinations/delusions, tremor Tachycardia, hyperpyrexia, diaphoresis High mortality rate

### Cardiovascular Complications

- HTN
- cardiomyopathy: SOB, edema
- dysrhythmias ("holiday heart")
  - atrial fibrillation (most common), atrial flutter, SVT, VT (especially Torsades if hypomagnesemic/hypokalemic)

### Metabolic Abnormalities

- alcoholic ketoacidosis
  - anion gap (AG) metabolic acidosis, urine ketones, low glucose and normal osmolality
  - history of chronic alcohol intake with abrupt decrease/cessation
  - malnourished, abdominal pain with nausea and vomiting
  - treatment: dextrose, thiamine (100 mg IM/IV prior to dextrose), volume repletion (with NS)
  - generally resolves in 12-24 h
- other alcohols
  - ethylene glycol → CNS, CVS, renal findings
  - methanol
    - ♦ early: lethargy, confusion
    - ♦ late: headache, visual changes, N/V, abdominal pain, tachypnea
  - both produce severe metabolic acidosis with anion gap (as the alcohol is metabolized) and osmolar gap (initially after ingestion but before metabolism)



Alcohol levels correlate poorly with intoxication.



Alcohol intoxication may invalidate informed consent.



### CIWA Withdrawal Symptoms

- Nausea and vomiting
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Visual disturbances
- Tactile disturbances
- Auditory disturbances
- Headache
- Disorientation

10 symptoms each scored out of 7 except orientation is out of 4.



### Common Deficiencies

- Thiamine
- Niacin
- Folate
- Glycogen
- Magnesium
- Potassium

- EtOH co-ingestion is protective
- treatment
  - ♦ urgent hemodialysis required
  - ♦ fomepizole 15 mg/kg IV bolus OR EtOH 10% IV bolus and infusion to achieve blood level of 22 mmol/L (EtOH loading may be done PO)
  - ♦ consider folic acid for methanol and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites
- other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

### Gastrointestinal Abnormalities

- gastritis
  - common cause of abdominal pain and GI bleed in chronic alcohol users
- pancreatitis
  - serum amylase very unreliable in patients with chronic pancreatitis, may need serum lipase
  - hemorrhagic form (15%) associated with increased mortality
  - fluid resuscitation very important
- hepatitis
  - AST/ALT ratio >2 suggests alcohol as the cause as well as elevated GGT with acute ingestion
- peritonitis/spontaneous bacterial peritonitis
  - leukocytosis, fever, generalized abdominal pain/tenderness
  - occasionally accompanies cirrhosis
  - paracentesis for diagnosis (common pathogens: *E. coli*, *Klebsiella*, *Streptococcus*)
- GI bleeds
  - most commonly gastritis or ulcers, even if patient known to have varices
  - consider Mallory-Weiss tear secondary to retching
  - often complicated by underlying coagulopathies
  - minor: treat with antacids
  - severe or recurrent: endoscopy

### Disposition

- before patient leaves ED ensure:
  - stable vital signs, can walk unassisted, fully oriented
- offer social services to find shelter or detox program
- ensure patient can obtain any medications prescribed and can complete any necessary follow-up

## Approach to the Overdose Patient



### History

- age, weight, underlying medical problems, medications
- substance and how much
- time since exposure determines prognosis and need for decontamination, symptoms since
- route
- intention, suicidality

### Physical Examination

- focus on: ABCs, LOC/GCS, vitals, pupils



#### Principles of Toxicology

4 principles to consider with all ingestions:

- Resuscitation (ABCs)
- Screening (toxidrome? clinical clues?)
- Decrease absorption of drug
- Increase elimination of drug



#### Suspect Overdose when:

- Altered level of consciousness/coma
- Young patient with life-threatening dysrhythmia
- Trauma patient
- Bizarre or puzzling clinical presentation

## ABCs of Toxicology

- basic axiom of care is symptomatic and supportive treatment
  - address underlying problem only once patient is stable
  - A Airway (consider stabilizing the C-spine)
  - B Breathing
  - C Circulation
  - D1 Drugs
    - ACLS as necessary to resuscitate the patient
    - universal antidotes
  - D2 Draw bloods
  - D3 Decontamination (decrease absorption)
  - E Expose (look for specific toxidromes)/Examine the patient
  - F Full vitals, ECG monitor, Foley, x-rays
  - G Give specific antidotes and treatments
- Go back and reassess  
Call poison information centre  
Obtain corroborative history from family, bystanders



## D1 – Universal Antidotes

- treatments that will not harm patients and may be essential

### Dextrose (glucose)

- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W
- children: 0.25 g/kg (2-4 mL/kg) IV of D25W

### Oxygen

- do not deprive a hypoxic patient of oxygen no matter what the antecedent medical history (i.e. even COPD with CO<sub>2</sub> retention)
- if depression of hypoxic drive, intubate and ventilate
- exception: paraquat or diquat (herbicides) inhalation or ingestion (oxygen radicals increase morbidity)

### Naloxone (central $\mu$ -receptor competitive antagonist, shorter $t_{1/2}$ than naltrexone)

- antidote for opioids: administration is both diagnostic and therapeutic (1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    - ♦ 2 mg initial bolus IV/IM/SL/SC or via ETT (ETT dose = 2-2.5x IV dose)
    - ♦ if no response after 2-3 min, increase dose by 2 mg increments until a response or to max 10 mg
    - ♦ known chronic user, suspicious history, or evidence of track marks, give 0.01 mg/kg
  - child
    - ♦ 0.01 mg/kg initial bolus IV/IO/ETT
    - ♦ 0.1 mg/kg if no response and opioid still suspected to max of 10 mg
- maintenance dose
  - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
  - ♦ hourly infusion rate at 2/3 of initial dose that produced patient arousal

### Thiamine (Vitamin B1)

- 100 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke's encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke's encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine unavailable
- must assume all undifferentiated comatose patients are at risk



#### Universal Antidotes

##### DON'T

- Dextrose
- Oxygen
- Naloxone
- Thiamine (must give BEFORE dextrose)



#### Populations at Risk for Thiamine Deficiency

- Alcoholics
- Anorexics
- Hyperemesis of pregnancy
- Malnutrition states



Administration of naloxone can cause opioid withdrawal in chronic users.

**Minor** withdrawal may present as lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, HTN, and tachycardia.

**Severe** withdrawal may present as hot and cold flashes, arthralgias, myalgias, N/V, and abdominal cramps.

## D2 – Draw Bloods

- essential tests (see Table 28)
  - CBC, electrolytes, BUN/creatinine, glucose, INR/PTT, osmolality
  - ABGs, measure O<sub>2</sub> sat
  - acetylsalicylic acid (ASA), acetaminophen, EtOH levels
- potentially useful tests
  - drug levels – this is NOT a serum drug screen
  - Ca<sup>2+</sup>, Mg<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup>
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical presentation

### Serum Drug Levels

- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only)

Table 27. Toxic Gaps (see also [Nephrology, NP14](#))

<b>METABOLIC ACIDOSIS</b>	
<b>Increased AG:</b> "MUDPILES CAT" (* = toxic)	<b>Increased POG:</b> "MAE DIE" (if it ends in "-ol", it will likely increase the POG)
Methanol*	Methanol
Uremia	Acetone
Diabetic ketoacidosis/Starvation ketoacidosis	Ethanol
Phenformin*/Paraldehyde*	Diuretics (glycerol, mannitol, sorbitol)
Isoniazid, Iron, Ibuprofen	Isopropanol
Lactate (anything that causes seizures or shock)	Ethylene glycol
Ethylene glycol*	
Salicylates*	
Cyanide, carbon monoxide*	Note: normal osmolar gap does not rule out toxic alcohol; only an elevated gap is helpful
Alcoholic Ketoacidosis	
Toluene, theophylline*	
<b>Decreased AG</b>	<b>Increased O<sub>2</sub> saturation gap</b>
Electrolyte imbalance (increased Na <sup>+</sup> /K <sup>+</sup> /Mg <sup>2+</sup> )	Carboxyhemoglobin
Hypoalbuminemia (50% fall in albumin ~5.5 mmol/L decrease in the AG)	Methemoglobin
Lithium, bromine elevation	Sulfmethemoglobin
Paraproteins (multiple myeloma)	
<b>Normal AG</b>	
High K <sup>+</sup> : pyelonephritis, obstructive nephropathy, renal tubular acidosis (RTA), IV, TPN	
Low K <sup>+</sup> : small bowel losses, acetazolamide, Renal Tubular Acidosis I, II	



**Plasma Osmolar Gap (POG)**  
 = (2 Na<sup>+</sup> + glucose + urea) – plasma osmolarity  
 "2 salts and a sugar BUN" – plasma osmolarity  
 Normal POG <10 mOsm/kg



**Anion Gap (AG)**  
 = Na<sup>+</sup> – Cl<sup>-</sup> – HCO<sub>3</sub><sup>-</sup>  
 Normal AG ≤12 mM/L

Table 28. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

Test	Finding	Selected Causes
<b>ABG</b>	Hypoventilation (↑ pCO <sub>2</sub> ) Hyperventilation (↓ pCO <sub>2</sub> )	CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, EtOH) Salicylates, CO, other asphyxiants
<b>Electrolytes</b>	↑ AGMA Hyperkalemia Hypokalemia	"MUDPILES CAT": see "Metabolic Acidosis", ER50 Digitalis glycosides, fluoride, potassium Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin
<b>Glucose</b>	Hypoglycemia	Oral hypoglycemia agents, insulin, EtOH, ASA
<b>Osmolality and Osmolar Gap</b>	Elevated osmolar gap	"MAE DIE": see "Toxic Gaps", above
<b>ECG</b>	Wide QRS complex Prolonged QT interval Atrioventricular block	TCAs, quinidine, other class Ia and Ic antidysrhythmic agents Quinidine and related antidysrhythmics, terfenadine, astemizole, antipsychotics Ca <sup>2+</sup> antagonists, digitalis glycosides, phenylpropanolamine
<b>Abdominal X-Ray</b>	Radiopaque pills or objects	"CHIPES": Calcium, Chloral hydrate, CCl <sub>4</sub> , Heavy metals, Iron, Potassium, Enteric coated Salicylates, and some foreign bodies
<b>Serum Acetaminophen</b>	Elevated level (>140 mg/L or 1000 μmol/L 4 h after ingestion)	May be only sign of acetaminophen poisoning

## D3 – Decontamination and Enhanced Elimination

### Ocular Decontamination

- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

### Dermal Decontamination (wear protective gear)

- remove clothing, brush off toxic agents, irrigate all external surfaces

### Gastrointestinal Decontamination

- single dose activated charcoal (SDAC) (see Table 31 for drug toxidromes that are treated with charcoal)
  - adsorption of drug/toxin to AC prevents availability
  - contraindications: caustics, SBO, perforation
  - dose: 10 g/g drug ingested or 1g/kg body weight
  - odourless, tasteless, prepared as slurry with H<sub>2</sub>O
- whole bowel irrigation
  - 500 mL/h (child) to 2000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
  - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated



**Substances NOT Adsorbed by Activated Charcoal**

- Lithium
- Iron
- Alcohols
- Lead
- Caustics

- indications
  - ♦ awake, alert, can be nursed upright OR intubated and airway protected
  - ♦ delayed release product
  - ♦ drug/toxin not bound to charcoal
  - ♦ drug packages (if any evidence of breakage → emergency surgery)
  - ♦ recent toxin ingestion
- contraindications
  - ♦ evidence of ileus, perforation, or obstruction
- surgical removal in extreme cases
  - indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
- no evidence for the routine use of cathartics (i.e. ipecac)

### Urine Alkalinization

- may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
- weakly acidic substances can be trapped in alkali urine (pH >7.5) to increase elimination

### Multidose Activated Charcoal (MDAC)

- may be used for: carbamazepine, phenobarbital, quinine, theophylline
- for toxins which undergo enterohepatic recirculation
- removes drug that has already been absorbed by drawing it back into GI tract
- various regimens: 12.5 g (1/4 bottle) PO q1h or 25 g (1/2 bottle) PO q2h until non-toxic

### Hemodialysis

- indications/criteria for hemodialysis
  - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution ( $V_d$ ) or rapid plasma equilibration
  - removal of toxin will cause clinical improvement
  - advantage is shown over other modes of therapy
  - predicted that drug or metabolite will have toxic effects
  - impairment of normal routes of elimination (cardiac, renal, or hepatic)
  - clinical deterioration despite maximal medical support
- useful for the following toxins:
  - methanol
  - ethylene glycol
  - salicylates
  - lithium
  - phenobarbital
  - chloral hydrate (→ trichloroethanol)
- others include theophylline, carbamazepine, valproate, methotrexate



#### Position Paper Update: Ipecac Syrup for Gastrointestinal Decontamination

*Clin Toxicol* 2013;51:134-139

**Study:** Systematic review of 12 new studies (2003-2011) and summary of older studies (animal studies, volunteer studies, marker studies, case reports).

**Conclusions:** There is debate in the literature as to whether or not the use of ipecac should be completely abandoned, or whether it may remain useful in certain special circumstances. Concerns regarding the use of ipecac include the variability of its effects depending on elapsed time of administration and its interference with other treatments such as activated charcoal. Furthermore, ipecac use has a number of side effects such as diarrhea, drowsiness and prolonged vomiting, as well as some rare side effects which may contribute to death. Despite these, ipecac has a high margin of safety.

While routine administration of ipecac is not appropriate, it may be beneficial in certain circumstances. For example, its use may be considered when there is a substantial risk of serious toxicity, there are no contraindications (such as high risk of aspiration), no alternative treatment option exists (or when the administration of ipecac will have no effect on the alternative treatment option) and there can be timely delivery of ipecac (<90 min).

## E – Expose and Examine the Patient

- vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours and CNS
- head-to-toe survey including
  - C-spine
  - signs of trauma, seizures (incontinence, “tongue biting”, etc.), infection (meningismus), chronic alcohol/drug abuse (track marks, nasal septum erosion)
- mental status

**Table 29. Specific Toxicities**

Toxidrome	Overdose Signs and Symptoms	Examples of Drugs	
Anticholinergics	Hyperthermia	“Hot as a hare”	Antidepressants (e.g. TCAs)
	Dilated pupils	“Blind as a bat”	Cyclobenzaprine (Flexeril®)
	Dry skin	“Dry as a bone”	Carbamazepine
	Vasodilation	“Red as a beet”	Antihistamines (e.g. diphenhydramine)
	Agitation/hallucinations	“Mad as a hatter”	Antiparkinsonians
	Ileus	“The bowel and bladder	Antipsychotics
	Urinary retention	lose their tone and the	Antispasmodics
	Tachycardia	heart goes on alone”	Belladonna alkaloids (e.g. atropine)
Cholinergics	“DUMBELS”		Natural plants: mushrooms, trumpet flower
	Diaphoresis, Diarrhea, Decreased blood pressure		Anticholinesterases: physostigmine,
	Urination		Insecticides (organophosphates, carbamates)
	Miosis		Nerve gases
	Bronchospasm, Bronchorrhea, Bradycardia		
	Emesis, Excitation of skeletal muscle		
	Lacrimation		
	Salivation, Seizures		



**Table 29. Specific Toxidromes** (continued)

Toxidrome	Overdose Signs and Symptoms	Examples of Drugs
<b>Extrapyramidal</b>	Dysphonia, dysphagia Rigidity and tremor Motor restlessness, crawling sensation (akathisia) Constant movements (dyskinesia) Dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis)	Major tranquilizers Antipsychotics
<b>Hemoglobin Derangements</b>	Increased respiratory rate Decreased level of consciousness Seizures Cyanosis unresponsive to O <sub>2</sub> Lactic acidosis	Carbon monoxide poisoning (carboxyhemoglobin) Drug ingestion (methemoglobin, sulfmethemoglobin)
<b>Narcotic Opioids, Sedative/Hypnotics, EtOH</b>	Hypothermia Hypotension Respiratory depression Dilated or constricted pupils (pinpoint in opioid OD) CNS depression	EtOH Benzodiazepines Opioids (morphine, heroin, fentanyl, etc.) Barbiturates Gamma hydroxybutyrate
<b>Sympathomimetics</b>	Increased temperature CNS excitation (including seizures) Tachycardia, hypertension Nausea and vomiting Diaphoresis Dilated pupils	Amphetamines, caffeine, cocaine, LSD, phencyclidine Ephedrine and other decongestants Thyroid hormone Sedative or EtOH withdrawal
<b>Serotonin Syndrome</b>	Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, hyperthermia, diarrhea, HTN	MAOI, TCA, SSRI, opiate analgesics Cough medicine, weight reduction medications

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

## F – Full Vitals, ECG Monitor, Foley, X-rays

## G – Give Specific Antidotes and Treatments

### Urine Alkalinization Treatment for ASA Overdose

- urine pH >7.5
- fluid resuscitate first, then 3 amps NaHCO<sub>3</sub>/litre of D5W @ 1.5 x maintenance
- add 20-40 mEq KCl/litre if patient is able to urinate

**Table 30. Protocol for Warfarin Overdose**

INR	Management: Consider Prothrombin Complex Concentrate (PCC) (Octaplex®, Beriplex®) for any elevated INR, AND either life-threatening bleeding or a plan for the patient to undergo a surgical procedure within the next 6 h
<5.0	Cessation of warfarin administration, observation, serial INR/PT
5.1–9.0	If no risk factors for bleeding, hold warfarin x 1-2 d and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding
9.1–20.0	Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary
>20.0	Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4h) if needed

**Table 31. Specific Antidotes and Treatments for Common Toxins – call local poison information centre for specific doses and treatment recommendations**

Toxin	Treatment	Considerations
<b>Acetaminophen</b>	Decontaminate (SDAC) N-acetylcysteine	Often clinically silent; evidence of liver/renal damage delayed > 24 h Toxic dose > 200 mg/kg (> 7.5 g adult) Monitor drug level 4 h post-ingestion; also liver enzymes, INR, PTT, BUN, Cr Hypoglycemia, metabolic acidosis, encephalopathy → poor prognosis
<b>Acute Dystonic Reaction</b>	Benzotropine: 1-2 mg IM/IV then 2 mg PO x 3 d OR Diphenhydramine 1-2 mg/kg IV, then 25 mg PO qid x 3 d	Benzotropine (Cogentin®) has euphoric effect and potential for abuse
<b>Anticholinergics</b>	Decontaminate (SDAC) Supportive care	Special antidotes available. Consult Poison Information Centre (PIC)

**Table 31. Specific Antidotes and Treatments for Common Toxins – (continued)**  
**call local poison information centre for specific doses and treatment recommendations**

Toxin	Treatment	Considerations
<b>ASA</b>	Decontaminate (SDAC) Alkalinize urine; want urine pH >7.5	Monitor serum pH and drug levels closely Monitor K <sup>+</sup> level; may require supplement for urine alkalinization Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or end-organ damage (i.e. unable to diurese)
<b>Benzodiazepines</b>	Decontaminate (SDAC) Flumazenil Supportive care	
<b>β-blockers</b>	Decontaminate (SDAC) Consider high dose insulin euglycemia therapy (HDIE) Some dialyzable, some use intralipids	Consult PIC
<b>Calcium Channel Blockers</b>	Decontaminate (SDAC) CaCl <sub>2</sub> 1-4 g of 10% sol'n IV if hypotensive Other: HDIE inotropes or intralipids	Order ECG, electrolytes (especially Ca <sup>2+</sup> , Mg <sup>2+</sup> , Na <sup>+</sup> , K <sup>+</sup> )
<b>Cocaine</b>	Decontaminate (SDAC) if oral Aggressive supportive care	β-blockers are contraindicated in acute cocaine toxicity Intralipid for life-threatening symptoms
<b>CO Poisoning</b>	See ER46 Supportive care 100% O <sub>2</sub>	
<b>Cyanide</b>	Hydroxocobalamin	
<b>Digoxin</b>	Decontaminate (SDAC) Digoxin-specific Ab fragments 10-20 vials IV if acute; 3-6 if chronic 1 vial (40 mg) neutralizes 0.5 mg of toxin	Use for life-threatening dysrhythmias unresponsive to conventional therapy, 6 h serum digoxin >12 nmol/L, initial K <sup>+</sup> >5 mM, ingestion >10 mg (adult)/>4 mg (child) Common dysrhythmias include VFib, VTach, and conduction blocks
<b>Ethanol</b>	Thiamine 100 mg IM/IV Manage airway and circulatory support	Hypoglycemia very common in children Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH Order serum EtOH level and glucose level; treat glucose level appropriately
<b>Ethylene Glycol/Methanol</b>	Fomepizole (4-methylpyrazole) 15 mg/kg IV load over 30 min, then 10 mg/kg q12h OR Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h	CBC, electrolytes, glucose, ethanol level Consider hemodialysis
<b>Heparin</b>	Protamine sulfate 25-50 mg IV	For unfractionated heparin overdose only
<b>Insulin IM/SC/Oral Hypoglycemic</b>	Glucose IV/PO/NG tube Glucagon: 1-2 mg IM (if no access to glucose)	Glyburide carries highest risk of hypoglycemia among oral agents Consider octreotide for oral hypoglycemics (50-100 µg SC q6h) in these cases; consult local PIC
<b>MDMA</b>	Decontaminate (SDAC), supportive care	Monitor CK; treat rhabdomyolysis with high flow fluids: aggressive external cooling for hyperthermia
<b>Opioids</b>	See Universal antidotes	
<b>TCAs</b>	Decontaminate (SDAC) Aggressive supportive care NaHCO <sub>3</sub> bolus for wide QRS/seizures	Flumazenil antidote contraindicated in combined TCA and benzodiazepine overdose Also consider cardiac and hypotension support, seizure control Intralipid therapy (consult local PIC)

## Disposition from the Emergency Department

- methanol, ethylene glycol
  - delayed onset, admit and watch clinical and biochemical markers
- TCAs
  - prolonged/delayed cardiotoxicity warrants admission to monitored (ICU) bed
  - if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  - sinus tachycardia alone (most common finding) with history of OD warrants observation in ED
- hydrocarbons/smoke inhalation
  - pneumonitis may lag 6-8 h
  - consider observation for repeated clinical and radiographic examination
- ASA, acetaminophen
  - if borderline level, get second level 2-4 h after first
  - for ASA must have at least 2 levels going down before discharge (3 levels minimum)
- oral hypoglycemics
  - admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  - observe asymptomatic patient for at least 8 h

### Psychiatric Consultation

- once patient medically cleared, arrange psychiatric intervention if required
- beware – suicidal ideation may not be expressed

# Psychiatric Emergencies

## Approach to Common Psychiatric Presentations

- see also [Psychiatry](#), PS2
- before seeing patient, ensure your own safety; have security/police available if necessary

### History

- safety
  - assess suicidality: suicidal ideation (SI), intent, plan, lethal means, past attempts
  - assess homicidality: homicidal ideation (HI), access to weapons, intended victim, history of violence
  - driving and children
  - command hallucinations
- identify current stressors and coping strategies
- mood symptoms: manic, depressive
- anxiety: panic attacks, generalized anxiety, phobias, OCD, PTSD
- psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
- substance use history: most recent use, amount, previous withdrawal reactions
- past psychiatric history, medications, adherence with medications
- medical history: obtain collateral if available

### Physical

- complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder
- mental status exam: general appearance, behavior, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability

### Investigations

- investigations vary with: age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
- as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum creatinine, BUN, osmolality
- blood levels of psychiatric medications
- CT head if suspect neurological etiology
- LP if indicated



#### Key Functions of Emergency Psychiatric Assessment

- Is the patient medically stable?
- Rule out medical cause
- Is psychiatric consult needed?
- Are there safety issues (SI, HI)?
- Is patient certifiable? (must demonstrate risk [present/past test] and apparent mental illness [future test])



#### Psychiatric review of systems for all patients with psychiatric presentations

##### MOAPS

Mood  
Organic  
Anxiety  
Psychosis  
Safety

## Acute Psychosis



### Differential Diagnosis

- primary psychotic disorder (e.g. schizophrenia)
- secondary to medical condition (e.g. delirium)
- drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
- infectious (CNS)
- metabolic (hypoglycemic, hepatic, renal, thyroid)
- structural (hemorrhage, neoplasm)

### Management

- violence prevention
  - remain calm, empathic and reassuring
  - ensure safety of staff and patients, have extra staff and/or security on hand
  - patients demonstrating escalating agitation or overt violent behavior may require physical restraint and/or chemical tranquilization (see *Violent Patient*, ER56)
- treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
  - benzodiazepines: lorazepam 2 mg PO, IM or SL
  - antipsychotics: olanzapine 5 mg PO, haloperidol 5 mg PO/IM
- treat underlying medical condition
- psychiatry or Crisis Intervention Team consult



## Suicidal Patient

### Epidemiology

- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr

### Management

- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), previous attempts
- admit if there is evidence of intent and organized plan, access to lethal means, psychiatric disorder, intoxication (suicidal ideation may resolve with few days of abstinence)
- patient may require certification if unwilling to stay voluntarily
- do not start long-term medications in the emergency department
- psychiatry or crisis team consult



#### High Risk Patients

##### SAD PERSONS

Sex = male  
Age >45 yr old  
Depression  
Previous attempts  
Ethanol use  
Rational thinking loss  
Suicide in family  
Organized plan  
No spouse, no support system  
Serious illness

## Violent Patient

### Differential Diagnosis

- rule out lethal organic cause (e.g. EtOH, drugs, and head injuries)

### Prevention

- be aware and look for prodromal signs of violence: anxiety, restlessness, defensiveness, verbal attacks
- try to de-escalate the situation: address the patient's anger, empathize

### Restraints

- pharmacological
  - often necessary – may mask clinical findings and impair exam
  - haloperidol 5-10 mg IM (be prepared for dystonic reactions, especially with multiple doses of neuroleptics over a short period) + lorazepam 2 mg IM/IV
  - look for signs of anticholinergic overdose first (see Table 29)
  - benzodiazepines best option if suspected substance-induced violence
- physical
  - present option to patient in firm but non-hostile manner
  - sufficient people to carry it out safely
  - restrain supine or on side; preferably 4-point restraints, never less than 2-points (opposite arm and leg)
  - suction and airway support available in case of vomiting
  - once restrained, search person/clothing for drugs and weapons

## Common Pediatric ER Presentations

### Modified Glasgow Coma Score

Table 32. Modified GCS

Modified GCS for Infants		
Eye Opening	Verbal Response	Motor Response
4 – spontaneously	5 – coos, babbles	6 – normal, spontaneous movement
3 – to speech	4 – irritable cry	5 – withdraws to touch
2 – to pain	3 – cries to pain	4 – withdraws to pain
1 – no response	2 – moans to pain	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response
Modified GCS for Children <4 years		
Eye Opening	Verbal Response	Motor Response
4 – spontaneously	5 – oriented, social, speaks, interacts	6 – normal, spontaneous movement
3 – to speech	4 – confused speech, disoriented, consolable	5 – localizes pain
2 – to pain	3 – inappropriate words, not consolable/aware	4 – withdraws to pain
1 – no response	2 – incomprehensible, agitated, restless, not aware	3 – decorticate flexion
	1 – no response	2 – decerebrate extension
		1 – no response



Any trauma or suspected trauma patient <1 yr of age with a large, boggy scalp hematoma requires ultrasound or CT.

## Respiratory Distress

- see also [Pediatrics](#), P92

### History and Physical Examination

- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
  - see [Pediatrics](#) Table 1, P3 for age specific vital signs
- pulsus paradoxus
- wheezing, grunting, vomiting

**Table 33. Stridorous Upper Airway Diseases: Diagnosis**

Feature	Croup	Bacterial Tracheitis	Epiglottitis <sup>1</sup>
Age Range (yr)	0.5-4	5-10	2-8
Prodrome	Days	Hours to days	Minutes to hours
Temperature	Low grade	High	High
Radiography	Steeple sign	Exudates in trachea	Thumb sign
Etiology	Parainfluenza	<i>S. aureus</i> /GAS	<i>H. influenzae</i> type b
Barky Cough	Yes	Yes	No
Drooling	Yes	No	Yes
Appear Toxic	No	Yes	Yes
Intubation/ICU	No	Yes	Yes
Antibiotics	No	Yes	Yes
NOTE:	Oral exam	Oral exam	No oral exam, consult ENT!

<sup>1</sup>Now rare with Hib vaccine in common use

### Management

- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - humidified O<sub>2</sub> should not be given (no evidence for efficacy)
  - racemic epinephrine q1h x 3 doses, observe for 'rebound effects' nebulized 1:1000 epi (racemic has limited availability)
  - dexamethasone x 1 dose
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
- bacterial tracheitis
  - start croup therapy, but may have poor response
  - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g. cloxacillin), pending C&S
- epiglottitis
  - 4 D's: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
  - do not examine oropharynx or agitate patient
  - immediate anesthesia, ENT call – intubate
  - then IV fluids, antibiotics, blood cultures
- asthma
  - supplemental O<sub>2</sub> if saturation <90% or PaO<sub>2</sub> <60%
  - bronchodilator therapy: salbutamol (Ventolin®) 0.15 mg/kg by masks q20min x 3
  - add 250-500 µg ipratropium (Atrovent®) to first 3 doses salbutamol
  - give corticosteroid therapy as soon as possible after arrival (prednisolone 2 mg/kg, dexamethasone 0.3 mg/kg)
  - if critically ill, not responding to inhaled bronchodilators or steroids: give IV bolus, then infusion of MgSO<sub>4</sub>
  - IV β<sub>2</sub>-agonists if critically ill and not responding to above



#### In Pediatric Respiratory Distress, Must also Rule Out:

- Anaphylaxis
- Foreign body
- Pneumonia
- Bronchiolitis



#### Admission Criteria for Croup

- Stridor at rest or significant respiratory distress
- Relapse after 2 doses of epinephrine or incomplete response
- Co-morbid respiratory or underlying condition



#### Admission Criteria for Asthma

- Respiratory distress 6 h after steroids
- Ventolin required >q3h
- Need for supplemental oxygen
- Consider if previous ICU admission
- Significant fatigue or lethargy

## Febrile Infant and Febrile Seizures

### FEBRILE INFANT

- see also [Pediatrics](#), P54
- for fever  $>38^{\circ}\text{C}$  without obvious focus
  - $<28$  d
    - ♦ admit
    - ♦ full septic work up (CBC and differential, blood C&S, urine C&S, LP  $\pm$  stool C&S, CXR if indicated)
    - ♦ treat empirically with broad spectrum IV antibiotics
  - 28-90 d
    - ♦ as above unless infant meets Rochester criteria (see sidebar), investigate as indicated by history and physical
  - $>90$  d
    - ♦ toxic: admit, treat, full septic workup
    - ♦ non-toxic and no focus: investigate as indicated by history and physical

### FEBRILE SEIZURES

- see also [Pediatrics](#), P87

#### Etiology

- children aged 6 mo to 6 yr with fever or history of recent fever
- simple vs. complex febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- relatively well looking after seizure

#### Investigations and Management

- if it is a febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
  - note: may also have fever but may not meet criteria for febrile seizure
- $\pm$  EEG (especially if first seizure), head U/S (if fontanelle open)

Table 34. Simple vs. Complex Febrile Seizures

Characteristic	Simple	Complex
Duration	$<15$ min	$>15$ min
Type of Seizure	Generalized	Focal features
Frequency	1 in 24 h	$>1$ in 24 h



#### Rochester Criteria for Febrile Infants Age 28-90 Days Old

- Non-toxic looking
- Previously well ( $>37$  wk GA, home with mother, no hyperbilirubinemia, no prior antibiotics or hospitalizations, no chronic/underlying illness)
- No skin, soft tissue, bone, joint, or ear infection on physical exam
- WBC 5000-15,000, bands  $<1500$ , urine  $<10$  WBC/HPF, stool  $<5$  WBC/HPF



## Abdominal Pain

- see also [Pediatrics](#), P38

### History

- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake

### Physical Examination

- HEENT, respiratory, abdominal exam including DRE, testicular/genital exam

Table 35. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents

Medical	Surgical
Colic	Malrotation with volvulus
UTI	Hirschsprung's disease
Constipation	Necrotizing enterocolitis
Gastroenteritis	Incarcerated hernia
Sepsis	Intussusception
HSP (Henoch Schonlein purpura)	Duodenal atresia
Inflammatory Bowel Disease	Appendicitis
HUS (Hemolytic Uremic Syndrome)	Cholecystitis
Pneumonia	Pancreatitis
Strep Throat	Testicular torsion
SCD crisis	Ectopic pregnancy
DKA	Trauma
Functional	Pyloric stenosis

\*Remember to keep an index of suspicion for child abuse



#### Red Flags for Abdominal Pain

- Significant weight loss or growth retardation (need growth chart)
- Fever
- Joint pain with objective physical findings
- Rash
- Rectal bleeding
- Rebound tenderness and radiation of pain to back, shoulders or legs
- Pain wakes from sleep
- Severe diarrhea and encopresis

## Common Infections

- see also [Pediatrics](#), P58



**Table 36. Antibiotic Treatment of Pediatric Bacterial Infections**

Infection	Pathogens	Treatment
<b>MENINGITIS SEPSIS</b>		
Neonatal	GBS, <i>E.coli</i> , <i>Listeria</i> , Gram-negative bacilli	ampicillin + cefotaxime
1-3 mo	Same pathogens as above and below	ampicillin + cefotaxime + vancomycin
>3 mo	<i>S. pneumoniae</i> , <i>H. influenzae</i> type b (>5 yr), meningococcus	ceftriaxone + vancomycin
<b>OTITIS MEDIA</b>		
1st line	<i>S. pneumoniae</i> , <i>H. influenzae</i> type b, <i>M. Catarrhalis</i>	amoxicillin 80-90 mg/kg per day
2nd line		clarithromycin 15 mg/kg/d bid (for penicillin allergy)
Treatment failure		90 mg/kg/d amoxicillin and 6.4 mg/kg/d clavulanate divided into bid dosage
<b>STREP PHARYNGITIS</b>		
	Group A $\beta$ -hemolytic <i>Streptococcus</i>	penicillin/amoxicillin or erythromycin (penicillin allergy)
<b>UTI</b>		
	<i>E. coli</i> , <i>Proteus</i> , <i>H. influenzae</i> , <i>Pseudomonas</i> , <i>S. saprophyticus</i> , <i>Enterococcus</i> , GBS	Oral: cephalexin (older children) IV: ampicillin and aminoglycoside
<b>PNEUMONIA</b>		
1-3 mo	Viral, <i>S. pneumoniae</i> , <i>C. trachomatis</i> , <i>B. pertussis</i> , <i>S. aureus</i> , <i>H. influenzae</i>	cefuroxime $\pm$ macrolide (erythromycin) OR ampicillin $\pm$ macrolide
3 mo-5 yr	Viral, <i>S. pneumoniae</i> , <i>S. aureus</i> , <i>H. influenzae</i> , <i>Mycoplasma pneumoniae</i>	ampicillin/amoxicillin or cefuroxime
>5 yr	As above	ampicillin/amoxicillin + macrolide or cefuroxime + macrolide

## Child Abuse and Neglect

- see also [Pediatrics](#), P14
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - head injuries: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken Baby Syndrome: diffuse brain injury, subdural/subarachnoid hemorrhage, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures age <1 yr of age, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - genitourinary/gastrointestinal injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea



### Presentation of Neglect

- Failure to thrive, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents

## Procedural Sedation

- procedural sedation: the technique of sedative or dissociative agent administration with or without analgesics to induce a state that allows a patient to tolerate an unpleasant or painful procedure while maintaining all protective cardiorespiratory functions (i.e. a depressed level of consciousness without loss of a patient's protective airway reflexes)
  - must weigh degree of pain and expected relief versus risk/complications of sedation and procedure

### Requirements for Safe Procedural Sedation in the Emergency Department

- airway suitable for safe intubation and ventilation
- appropriate equipment/personnel available
- intact and functioning cardiorespiratory and neurological system
- ideally, NPO for minimum 4-6 h
- anesthetic history and drug allergies, including manifestations
- appropriate IV access, monitoring (oxygen saturation, BP, HR, etc.)
- informed consent obtained

### Common Procedural Sedation Medications (titrate to effect)

- see *Common Medications*, below



#### Examples that may Require Sedation

- Setting fractures
- Reducing dislocations
- Draining abscesses
- Exploring wounds/ulcers/superficial infections
- Endoscopic examination
- May also be required to reduce patient agitation if imaging is acutely required

## Common Medications

Table 37. Commonly Used Medications

Drug	Dosing Schedule	Indications	Comments
Acetaminophen	325-650 mg PO q4-6h prn	Pain control	Max 4 g daily
Activated charcoal	30-100 g PO in 250 mL H <sub>2</sub> O	Poisoning/overdose	
ASA	325-650 mg PO q4h max 4g/d stroke/MI risk: 81-325 mg PO OD 160 mg chewed	Pain control Cardiac prevention Acute Coronary Syndrome	
β-blockers (metoprolol)	5 mg slow IV q5min x 3 if no contraindications	Acute MI	
Diazepam	anxiety: 2-10 mg PO tid/qid alcohol withdrawal: 10-20 mg PO/IV q1h titrated to signs/symptoms	Anxiety Alcohol withdrawal	
Enoxaparin	1 mg/kg SC bid	Acute MI	
Epinephrine	anaphylaxis: 0.1-0.5 mg IM; can repeat q10-15min	Anaphylaxis	Max 1 mg/dose
Fentanyl	0.5-1.0 µg/kg IV	Procedural sedation	Very short acting narcotic (complication=apnea)
Flumazenil	0.3 mg IV bolus q5min x 3doses	Reversal of procedural sedation	Benzodiazepine antagonist NB don't use in chronic benzodiazepine user
Furosemide (Lasix®)	CHF: 40-80 mg IV HTN: 10-40 mg PO bid	CHF HTN	Monitor for electrolyte imbalances
Glucose	0.5-1.0 g/kg (1-2 mL/kg) IV of D50W	Hypoglycemia/DKA	
Haloperidol	2.5-5.0 mg PO/IM initial effective dose 6-20 mg/d	Psychosis	Monitor with Parkinson's; results in CNS depression
Ibuprofen	200-800 mg PO tid prn max 1200 mg/d	Mild to moderate acute pain Analgesia and anti-inflammatory properties	
Insulin	bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per hour	Hyperglycemia	Monitor blood glucose levels Consider K <sup>+</sup> replacement, also measure blood glucose levels before administration
Ipratropium bromide	2-3 puffs inhaled tid-qid, max 12 puffs/d	Asthma	Contraindicated with peanut/soy allergy Caution with narrow-angle glaucoma
Lidocaine with epi	max 7 mg/kg SC	Local anesthetic	Not to be used in fingers, nose, toes, penis, ears
Lidocaine w/o epi	max 5 mg/kg SC	Local anesthetic	
Lorazepam	anxiety: 0.5-2 mg PO/IM/IV q6-8h status epilepticus; 4 mg IV repeat up to q5min	Anxiety Status epilepticus	
Midazolam	50 µg/kg IV	Procedural sedation	Short acting benzodiazepine (complication=apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation

**Table 37. Commonly Used Medications** (continued)

Drug	Dosing Schedule	Indications	Comments
Morphine	15-30 mg PO q8-12h 0.1-0.2 mg/kg max 15 mg IV q4h	Mild to moderate acute/chronic pain Prescribed in combination with NSAIDs or acetaminophen	GI and constipation side effects DO NOT CRUSH, CUT or CHEW
Naloxone	0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg	Comatose patient Opioid overdose Reversal in procedural sedation	
Nitroglycerin	acute angina: 0.3-0.6 mg SL q5min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5min	Angina Acute MI	Not to be used with other anti-hypertensives Not in RV MI
Percocet 10/325®	1-2 tabs PO q6h prn	Moderate pain control	Oxycodone + acetaminophen Max 4 g acetaminophen daily
Phenytoin	Status epilepticus: see Table 14	Status epilepticus	Begin maintenance dose 12 h after loading dose Continuous ECG, BP monitoring mandatory
Polysporin®	Apply to affected area bid-tid	Superficial infections	
Propofol	0.25-1 mg/kg IV	Procedural sedation	Short acting Anesthetic/sedative (complication = apnea, decreased BP)
Salbutamol	2 puffs inhaled q4-6h (4 yr) max 12 puffs/d	Asthma	Caution with cardiac abnormalities
Thiamine	Wernicke's encephalopathy: 100 mg IV/IM initially then 50-100 mg IM/IV OD PO x 3d	To treat/prevent Wernicke's encephalopathy	Caution use in pregnancy
Tylenol #3®	1-2 tabs PO q4-6h prn	Pain control	Max 4 g acetaminophen daily

## References

### Books

- Andreoli TE, Carpenter CJ, Griggs RC, Benjamin LJ. Cecil's essentials of medicine, 8th ed. Saunders, 2010.  
 Barash PG, Cullen BF, Stoelting RK. Clinical anesthesia, 5th ed. Philadelphia: Lippincott, 2005.  
 Kalant H, Roschla W. Principles of medical pharmacology, 7th ed. New York: Oxford University Press, 2006.  
 Keim, Setal. Emergency medicine on call. McGraw Hill, 2004.  
 Marx (ed). Rosen's emergency medicine: concepts and clinical practice, 7th ed. Mosby, 2009.  
 Roberts JR, Hedges JR. Clinical procedures in emergency medicine, 5th ed. WB Saunders, 2009.  
 Tintinalli JE, Kelen GE. Emergency medicine: a comprehensive study guide, 7th ed. McGraw-Hill, 2004.

### Journal Articles

- American College of Emergency Physicians. Clinical policy for the initial approach to patients presenting with altered mental status. Ann Emerg Med 1999;33:251-280.  
 Bachmann LM, Kolb E, Koller MT, et al. Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot: systematic review. BMJ 2003;326:417.  
 Chu P. Blunt abdominal trauma: current concepts. Curr Orthopaed 2003;17:254-259.  
 Dargan P, Wallace C, Jones AL. An evidence based flowchart to guide the management of acute salicylate (Aspirin®) overdose. Emerg Med J 2002;19:206-209.  
 Elliott WJ. Hypertensive emergencies. Crit Care Clin 2001;17:435-451.  
 Frampton A. Reporting of gunshot wounds by doctors in emergency departments: A duty or a right? Some legal and ethical issues surrounding breaking patient confidentiality. Emerg Med J 2005;22:84-86.  
 Kline JA, Mitchell AM, Kabrhe C, Richman PB, Courtney DM. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost 2004;2:1247-1255.  
 Munro P. Management of eclampsia in the accident and emergency department. Emerg Med J 2000;7:7-11.  
 Perry JJ, et al. Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study. BMJ 2011;343:d4277.  
 Russell JA, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. NEJM 2008;358:877-887.  
 Sabatine MS, et al. Addition of clopidogrel to Aspirin® and fibrinolytic therapy for myocardial infarction with ST-segment elevation. NEJM 2005;352:1179-1189.  
 Soar J, et al. Emergency treatment of anaphylactic reactions: guideline for healthcare providers. Resuscitation 2008;77:157-169.  
 Stiell IG, et al. The Canadian CT head rule for patients with minor head injury. Lancet 2001;357:1391-1396.  
 Stiell IG, et al. The Canadian C-spine rule for radiography in alert and stable trauma patients. JAMA 2001;286:1841-1848.  
 Varon J, Marik P. The Diagnosis and management of hypertensive crises. Chest 2000;118:214-227.  
 Vidt DG. Emergency room management of hypertensive urgencies and emergencies. J Clin Hypertens 2004;6:520-525.  
 Warden C, et al. Evaluation and management of febrile seizures in the out-of-hospital and emergency department settings. Ann Emerg Med 2003;41:215-222.  
 Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the simpliRED d-dimer. J Thromb Haemost 2000;83:416-420.  
 Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model. Ann Int Med 2000;135:98-107.



Yayi Huang, Angela Liu and Anna Liu, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Julia Lowe and Dr. Phillip Segal, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Adrenal Cortex</b> . . . . .	<b>29</b>
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	Adrenocorticotropin Hormone (ACTH)	
Major Endocrine Organs		Adrenocortical Hormones	
<b>Dyslipidemias</b> . . . . .	<b>2</b>	Adrenocortical Functional Work-Up	
Overview of Lipid Transport		Mineralocorticoid Excess Syndromes	
Hypercholesterolemia		Cushing's Syndrome	
Hypertriglyceridemia (Elevated TG)		Congenital Adrenal Hyperplasia	
Combined Hyperlipidemia		Hyperandrogenism	
Dyslipidemia and the Risk for CAD		Adrenocortical Insufficiency	
Treatment of Dyslipidemias		<b>Adrenal Medulla</b> . . . . .	<b>36</b>
<b>Disorders of Glucose Metabolism</b> . . . . .	<b>6</b>	Catecholamine Metabolism	
Overview of Glucose Regulation		Pheochromocytoma	
Pre-Diabetes		<b>Disorders of Multiple Endocrine Glands</b> . . . .	<b>36</b>
Diabetes Mellitus (DM)		Multiple Endocrine Neoplasm (MEN)	
Treatment of Diabetes		<b>Calcium Homeostasis</b> . . . . .	<b>38</b>
Acute Complications		Hypercalcemia	
Macrovascular Complications		Hypocalcemia	
Microvascular Complications		Hyperphosphatemia	
Other Complications		Hypophosphotemia	
Hypoglycemia		Hypermagnesemia	
Metabolic Syndrome		Hypomagnesemia	
<b>Obesity</b> . . . . .	<b>FM7</b>	<b>Metabolic Bone Disease</b> . . . . .	<b>42</b>
<b>Pituitary Gland</b> . . . . .	<b>16</b>	Osteoporosis	
Pituitary Hormones		Osteomalacia and Rickets	
Growth Hormone (GH)		Renal Osteodystrophy	
Prolactin (PRL)		Paget's Disease of Bone	
Thyroid Stimulating Hormone (TSH)		<b>Male Reproductive Endocrinology</b> . . . . .	<b>47</b>
Adrenocorticotropin Hormone (ACTH)		Androgen Regulation	
Luteinizing Hormone (LH) and		Tests of Testicular Function	
Follicle Stimulating Hormone (FSH)		Hypogonadism and Infertility	
Antidiuretic Hormone (ADH)		Erectile Dysfunction	
Pituitary Pathology		Gynecomastia	
<b>Thyroid</b> . . . . .	<b>20</b>	<b>Female Reproductive Endocrinology</b> . . . . .	<b>GY4</b>
Thyroid Hormones		<b>Paraneoplastic Syndrome</b> . . . . .	<b>51</b>
Tests of Thyroid Function and Structure		<b>Common Medications</b> . . . . .	<b>52</b>
Thyrotoxicosis		Diabetes Medications	
Graves' Disease		Dyslipidemia Medications	
Subacute Thyroiditis		Thyroid Medications	
Toxic Adenoma/Toxic Multinodular Goitre		Metabolic Bone Disease Medications	
Thyrotoxic Crisis/Thyroid Storm		Adrenal Medications	
Hypothyroidism		<b>Landmark Endocrinology Trials</b> . . . . .	<b>56</b>
Hashimoto's Thyroiditis		<b>References</b> . . . . .	<b>57</b>
Myxedema Coma			
Sick Euthyroid Syndrome (SES)			
Non-Toxic Goitre			
Thyroid Nodules			
Thyroid Malignancies			

## Acronyms

[ ]	concentration	DHEA	dihydroepiandrosterone	HHS	hyperosmolar hyperglycemic state	PCOS	polycystic ovarian syndrome
Ab	antibody	DI	diabetes insipidus	HLA	human leukocyte antigen	POMC	pro-opiomelanocorticotropin
ACR	albumin-creatinine ratio	DKA	diabetic ketoacidosis	HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme A	PRL	prolactin
ACTH	adrenocorticotropic hormone	DM	diabetes mellitus	HPA	hypothalamic pituitary adrenal	PTH	parathyroid hormone
ADH	anti-diuretic hormone	DXM	dexamethasone	hs-CRP	highly sensitive C-reactive protein	PTU	propylthiouracil
AG	anion gap	ECF	extracellular fluid	ICF	intracellular fluid	PAD	peripheral arterial disease
BG	blood glucose	EtOH	ethanol	IDL	intermediate density lipoprotein	RAAS	renin-angiotensin-aldosterone system
BMD	bone mineral density	FBG	fasting blood glucose	IFG	impaired fasting glucose	RH	releasing hormone
BMI	body mass index	FFA	free fatty acids	IGT	impaired glucose tolerance	T <sub>3</sub>	triiodothyronine
CAD	coronary artery disease	FNA	fine needle aspiration	LCAT	Lecithin-cholesterol acyltransferase	T <sub>4</sub>	thyroxine
CAH	congenital adrenal hyperplasia	FSH	follicle stimulating hormone	LDL	low density lipoprotein	TBG	thyroid binding globulin
CHO	carbohydrates	GFR	glomerular filtration rate	LH	luteinizing hormone Lpipoprotein	TC	total cholesterol
CK	creatinine kinase	GH	growth hormone	MEN	multiple endocrine neoplasia	TG	triglycerides
CMV	cytomegalovirus	GHIH	growth hormone inhibiting hormone	MMI	methimazole	TRH	thyrotropin releasing hormone
CrCl	creatinine clearance	GRH	gonadotropin releasing hormone	MTC	medullary thyroid cancer	TSH	thyroid stimulating hormone
CRH	corticotropin releasing hormone	Hb	hemoglobin	NS	normal saline	VLDL	very low density lipoprotein
CVD	cardiovascular disease	hCG	human chorionic gonadotropin	OGTT	oral glucose tolerance test	WVC	waist circumference
DDAVP	desmopressin (1-deamino-8-D-arginine vasopressin)	HDL	high density lipoprotein				

## Basic Anatomy Review

### Major Endocrine Organs

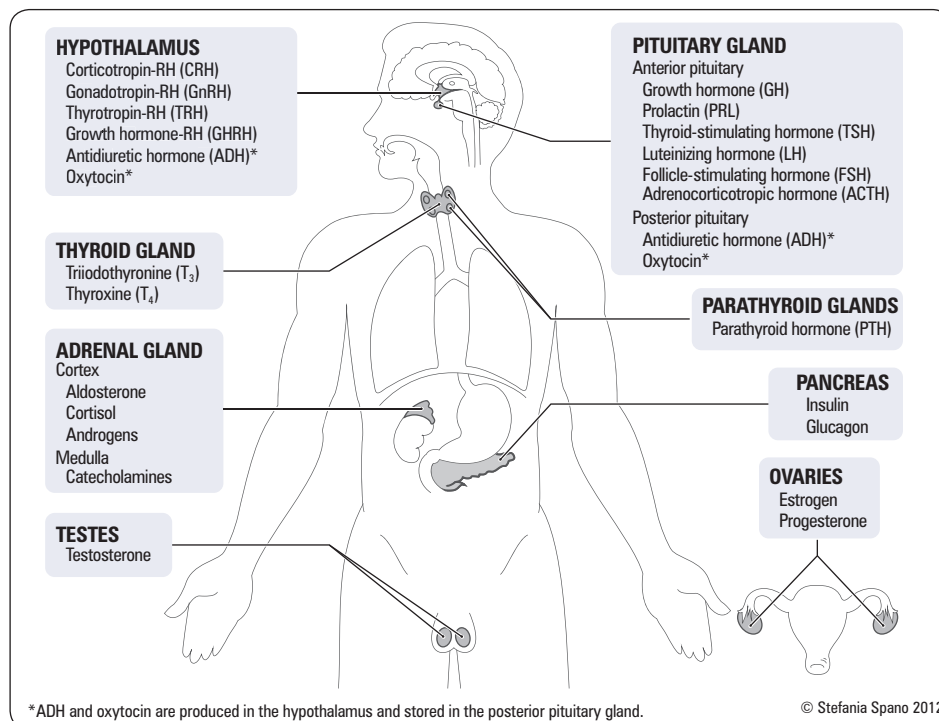


Figure 1. Endocrine system

## Dyslipidemias

### Definition

- metabolic disorders characterized by elevations of fasting plasma LDL-cholesterol, and/or triglycerides (TG), and/or low HDL-cholesterol

### Overview of Lipid Transport

- lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apoproteins and phospholipids
- lipoproteins transport lipids within the body
- apolipoproteins serve as enzyme co-factors, promote clearance of the particle by interacting with cellular receptors and stabilize the lipoprotein micelle



### GENERAL FUNCTION OF ORGANS

#### The Hypothalamic-Pituitary Axis

Information about cortical inputs, automatic function, environmental cues (light, temp) and peripheral hormonal feedback is synthesized at the coordinating centre of the endocrine system, the hypothalamus. The hypothalamus then sends signals to the pituitary to release hormones that affect the thyroid, adrenals, gonads, growth, milk production and water balance.

#### Anatomy ↔ Function

Hypothalamic hormones: small peptides, non-binding protein → rapid degradation  
High [ ] in pituitary-portal blood system  
Low [ ] in peripheral circulation  
Proximity of axis preserves the pulsatile output signals from the hypothalamic neurons.

#### Thyroid

Thyroid hormone is critical to 1) brain and somatic development in fetus and infants, 2) metabolic activity in adults, and 3) function of virtually every organ system.

#### Adrenal

Each gland, 6-8 g, has 1) a cortex with 3 layers that act like independent organs (zona glomerulosa → aldosterone, fasciculata → cortisol, reticularis → androgen and estrogen precursors), and 2) a medulla that acts like a sympathetic ganglion to store/synthesize adrenaline and noradrenaline.

#### Gonads

Bifunctional: sex steroid synthesis and gamete production.  
Sex steroids controls sexuality and affect metabolic and brain functions.

#### Parathyroid

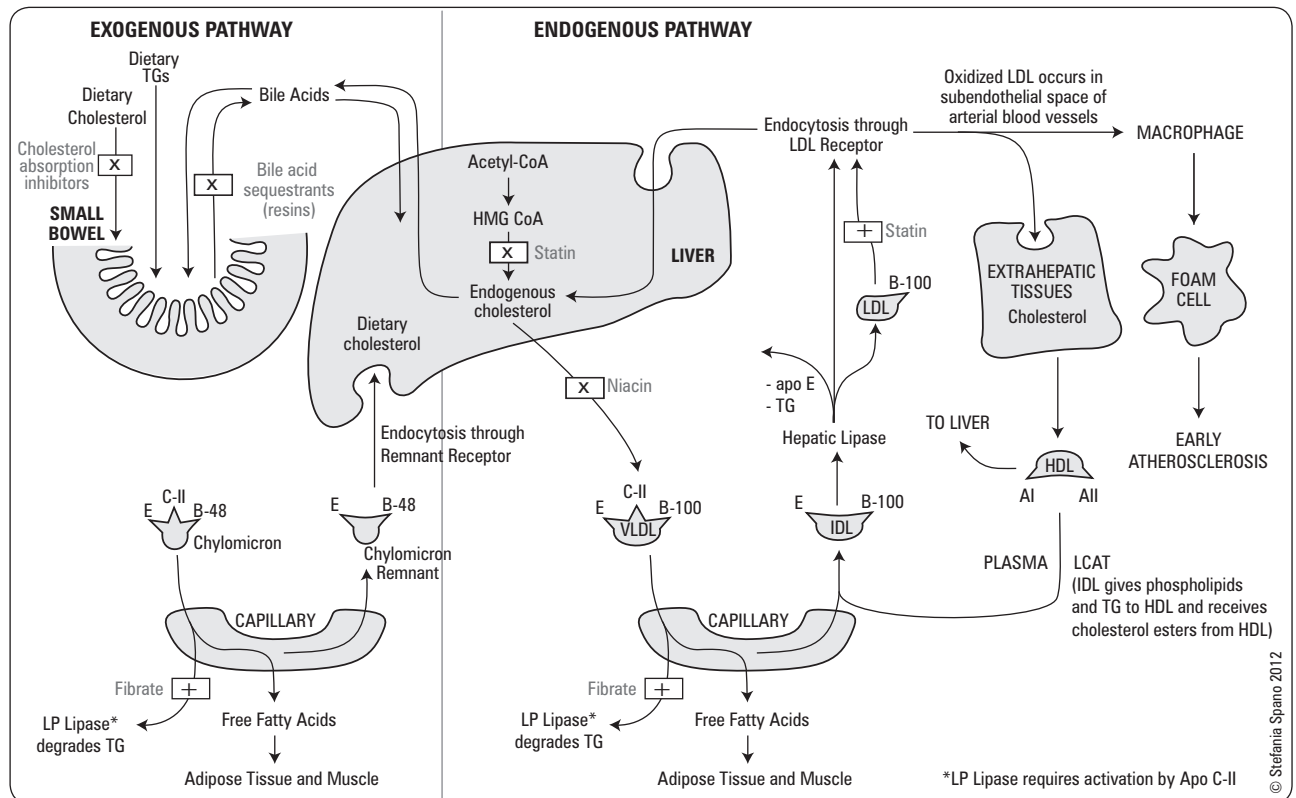
Synthesize and secrete PTH, a principle regulator of ECF Ca<sup>2+</sup>, regulated by [Ca<sup>2+</sup>], [Mg<sup>2+</sup>], 1,25(OH)<sub>2</sub>D (active metabolite of vit. D), and phosphate.

#### Pancreas

Endocrine islet β-cells produce insulin: oppose glucose production (glycogenolysis, gluconeogenesis), increase glucose uptake into muscle and fat. Glucagon, epinephrine, cortisol, and GH are counter regulatory.

**Table 1. Lipoproteins**

Lipoprotein	Apolipoproteins	Function
<b>Exogenous pathway</b>		
Chylomicron	B-48, C, E, A-I, A-II, A-IV	• Transports dietary TG from gut to adipose tissue and muscle
<b>Endogenous Pathway</b>		
VLDL	B-100, C, E	• Transports hepatic synthesized TG from liver to adipose tissue and muscle
IDL	B-100, E	• Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core • Enriched in cholesterol esters
LDL	B-100	• Formed by further removal of residual TG from IDL core by hepatic lipase resulting in greater enriched particles with cholesterol esters • Transports cholesterol from liver to peripheral tissues (gonads, adrenals)
HDL	A-I, A-II, C, E	• Transports cholesterol from peripheral tissues to liver • Acts as a reservoir for apolipoproteins

**Figure 2. Exogenous and endogenous biosynthetic lipid pathways**

## Hypercholesterolemia

### PRIMARY HYPERCHOLESTEROLEMIA

**Table 2. Primary Hypercholesterolemias**

Hypercholesterolemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Hypercholesterolemia	<ul style="list-style-type: none"> <li>1/500 in U.S. population</li> <li>Autosomal codominant with high penetrance</li> <li>More prevalent in French Canadian population</li> <li>Defect in the normal LDL receptor on cell membranes</li> </ul>	↑ LDL ↑ TC	<ul style="list-style-type: none"> <li>Tendinous xanthomatosis (achilles, patellar, and extensor tendons of hand)</li> <li>Arcus cornealis</li> <li>Xanthelasmata</li> <li>Heterozygotes: premature CAD, 50% risk of MI in men by age 30</li> <li>Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (&lt;20 y) if untreated</li> </ul>	<ul style="list-style-type: none"> <li>Heterozygotes: improvement of LDL with HMG CoA reductase inhibitors, often in combination with niacin ezetimibe or bile acid sequestrants</li> <li>Homozygotes: partial control with portacaval shunt or LDL apheresis in conjunction with niacin; large dose atorvastatin is modestly effective</li> </ul>
Polygenic Hypercholesterolemia	<ul style="list-style-type: none"> <li>Most common</li> <li>Few mild inherited defects in cholesterol metabolism</li> </ul>	↑ TC ↑ LDL	<ul style="list-style-type: none"> <li>Asymptomatic until vascular disease develops</li> <li>No xanthomata</li> </ul>	<ul style="list-style-type: none"> <li>HMG CoA reductase inhibitors, ezetimibe, niacin, bile acid sequesterant</li> </ul>

## SECONDARY HYPERCHOLESTEROLEMIA

### Etiology

- endocrine: hypothyroidism
- renal: nephrotic syndrome
- immunologic: monoclonal gammopathy
- hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)
- nutritional: diet, anorexia nervosa
- drugs: cyclosporin, anabolic steroids, carbamazepine

## Hypertriglyceridemia (Elevated TG)

### PRIMARY HYPERTRIGLYCERIDEMIA

Table 3. Primary Hypertriglyceridemias

Hypertriglyceridemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Lipoprotein Lipase Deficiency	• Autosomal recessive deficiency of lipoprotein lipase or its cofactor	↑ TG ↑ Chylomicrons Moderate ↑ in VLDL	<ul style="list-style-type: none"> <li>• Hepatosplenomegaly</li> <li>• Splenic infarct</li> <li>• Anemia, granulocytopenia, thrombocytopenia 2° to hypersplenism</li> <li>• Pancreatitis</li> <li>• Lipemia retinalis</li> <li>• Eruptive xanthomata</li> </ul>	<ul style="list-style-type: none"> <li>• Decrease dietary fat intake to &lt;10% of total calories</li> <li>• Decrease dietary simple carbohydrates</li> <li>• Cook with medium chain fatty acids</li> <li>• Abstain from EtOH</li> </ul>
Familial Hypertriglyceridemia	• Several genetic defects resulting in ↑ hepatic VLDL synthesis or ↓ removal of VLDL	↑ TG ↑ VLDL	<ul style="list-style-type: none"> <li>• Possible premature CAD</li> <li>• Develop syndrome of obesity, hypertriglyceridemia, hyperinsulinemia and hyperuricemia in early adulthood</li> </ul>	<ul style="list-style-type: none"> <li>• Decrease dietary simple carbohydrates and fat intake</li> <li>• Abstain from EtOH</li> <li>• Fibrates or niacin</li> </ul>



**Hypertriglyceridemia and Pancreatitis**  
Serum triglyceride levels >10 mmol/L increases the risk of developing pancreatitis (even some reports of TG >5 mmol/L).



**Low HDL**  
Common causes:  

- Obesity
- Physical inactivity
- Cigarette smoking
- Metabolic syndrome, Type 2 Diabetes Mellitus

### SECONDARY HYPERTRIGLYCERIDEMIA

#### Etiology

- endocrine: obesity/metabolic syndrome, hypothyroidism (more for high LDL, not TG), acromegaly, Cushing's syndrome, diabetes mellitus
- renal: chronic renal failure, polyclonal and monoclonal hypergammaglobulinemia
- hepatic: chronic liver disease, hepatitis, glycogen storage disease
- drugs: alcohol, corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
- other: pregnancy



**Side-effects of Atypical Anti-psychotics**  
Increased risk of:  

- Dyslipidemia
- Hypertension
- Metabolic syndrome
- Hyperglycemia

## Combined Hyperlipidemia

Table 4. Primary Combined Hyperlipidemias

Hyperlipidemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Combined Hyperlipidemia	• Over-population of VLDL and associated ↑ LDL 2° to excess hepatic synthesis of apolipoprotein B • Autosomal dominant	↑ TC + TG ↑ VLDL ↑ LDL	<ul style="list-style-type: none"> <li>• Xanthelasma</li> <li>• CAD and other vascular disease</li> </ul>	<ul style="list-style-type: none"> <li>• Weight reduction</li> <li>• Decrease simple carbohydrates, fat, cholesterol, and EtOH in diet</li> <li>• HMG CoA reductase inhibitors (statins)</li> <li>• Niacin, fibrates, ezetimibe</li> </ul>
Dysbetalipoproteinemia	• Abnormal apolipoprotein E	↑ TC + TG ↑ VLDL ↑ IDL	<ul style="list-style-type: none"> <li>• Tuberos, eruptive, palmar xanthomata</li> <li>• Impaired glucose tolerance</li> <li>• CAD and PAD</li> </ul>	<ul style="list-style-type: none"> <li>• Weight reduction</li> <li>• Decrease fat, cholesterol, and EtOH in diet</li> <li>• HMG CoA reductase inhibitors</li> <li>• Niacin, fibrates</li> </ul>

## Dyslipidemia and the Risk for CAD

- increased LDL is a major risk factor for atherosclerosis and CAD as LDL is the major atherogenic lipid particle
- increased HDL is associated with decreased cardiovascular disease and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3-9 mmol/L) is an independent risk factor for CAD, especially in people with diabetes mellitus and in post-menopausal women
- treatment of hypertriglyceridemia has not been shown to reduce CAD risk

### Screening

- screen men over age 40, women over age 50 or post-menopausal
- if following risk factors present, screen at any age:
  - diabetes
  - cigarette smoking
  - hypertension (sBP >140, dBP >90)
  - obesity
  - family history of premature coronary artery disease
  - clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
  - evidence of atherosclerosis
  - rheumatoid arthritis, SLE, psoriasis
  - HIV infection on highly active antiretroviral therapy (HAART)
  - chronic kidney disease (estimated GFR <60 mL/min/1.73 m<sup>2</sup>)
  - erectile dysfunction
- screen children with a family history of hypercholesterolemia or chylomicronemia

### Factors Affecting Risk Assessment

- metabolic syndrome
- apolipoprotein B (apo B):
  - each atherogenic particle (VLDL, IDL, LDL and lipoprotein A) contains one molecule of apo B
  - serum [apo B] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome
- C-reactive protein (hs-CRP) levels:
  - highly sensitive acute phase reactant
  - may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment



#### Treatment Effect

Each 1.0 mmol/L decrease in LDL corresponds to 20-25% relative risk reduction in cardiovascular disease.



#### For Statin Follow-Up

- Liver enzymes and lipid profile: liver enzymes measured at the beginning of treatment then once after therapy initiated. Lipids (once stabilized) measured annually. Order both if patient complains of jaundice, RUQ pain, dark urine
- CK at baseline and if patient complains of myalgia
- D/C statin if CK >10x upper limit of normal or patient has persistent myalgia

## Treatment of Dyslipidemias

### Approach to Treatment

For clinical guidelines see Can J Cardiol 2012;29:151-167

- estimate 10-yr risk of CAD using Framingham model
- establish treatment targets according to level of risk (see Table 5)

**Table 5. Target Lipids by Risk Group**

Level of Risk	Definition (10-yr Risk of CAD)	Initiate Treatment if:	Primary Target LDL-C	Alternate
High	<ul style="list-style-type: none"> <li>• Risk ≥20%, or</li> <li>• Clinical atherosclerosis</li> <li>• Abdominal aortic aneurysm</li> <li>• Diabetes &gt;15 yr duration and age older than 30 yr</li> <li>• Diabetes with age older than 40 yr</li> <li>• Microvascular disease</li> <li>• High risk kidney disease</li> <li>• High risk hypertension</li> </ul>	Consider treatment in all patients	≤2 mmol/L (78 mg/dL) or ≥50% ↓ in LDL	apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L
Moderate	Risk 10-19%	<ul style="list-style-type: none"> <li>• LDL &gt;3.5 mmol/L (136.5 mg/dL)</li> <li>• For LDL-C &lt;3.5 consider if: apo B ≥1.2 g/L or non-HDL-C ≥4.3 mmol/L</li> </ul>	≤2 mmol/L (78 mg/dL) or ≥50% ↓ in LDL	apo B <0.80 g/L or non-HDL-C ≤2.6 mmol/L
Low	Risk <10%	<ul style="list-style-type: none"> <li>• LDL ≥5.0 mmol/L (195 mg/dL)</li> <li>• Familial hypercholesterolemia</li> </ul>	≥50% ↓ in LDL	



#### Intensive Lipid Lowering in CAD: TNT

NEJM 2005;352:1425-1435

**Study:** Multicentre, randomized, double-blinded trial with median follow-up of 4.9 yr.

**Patients:** 10,001 patients with CAD and LDL-C <3.4 mmol/L.

**Intervention:** 80 mg versus 10 mg atorvastatin daily.

**Main outcomes:** Death from CAD, MI, cardiac arrest, or stroke.

**Results:** A primary event occurred in 8.7% of the patients receiving intensive therapy, compared to 10.9% of patients receiving standard therapy (RR 0.78, p<0.001). There was no difference in overall mortality. Incidence of persistent transaminase elevations was higher in the intensive therapy group (1.2% versus 0.2%, p<0.001).

**Conclusion:** Intensive statin therapy is associated with lower rates of CAD events than standard therapy, but also a higher rate of transaminase elevation.



#### Simvastatin to Lower CAD Risk – The Heart Protection Study (HPS)

Lancet 2002;360:7-22

**Study:** Randomized, double-blind, placebo-controlled trial (median follow-up 5.0 yr).

**Patients:** 20,536 patients with coronary disease, other occlusive arterial disease or diabetes (aged 40-80 yr) who had a total cholesterol level of ≥3.5 mmol/L.

**Intervention:** Simvastatin 40 mg/d or placebo.

**Main Outcomes:** Mortality, fatal or non-fatal vascular events.

**Results:** The use of simvastatin significantly decreased total mortality (12.9 vs. 14.7, p=0.0003) and the first event rate of any cardiovascular event by 25% (p<0.0001).

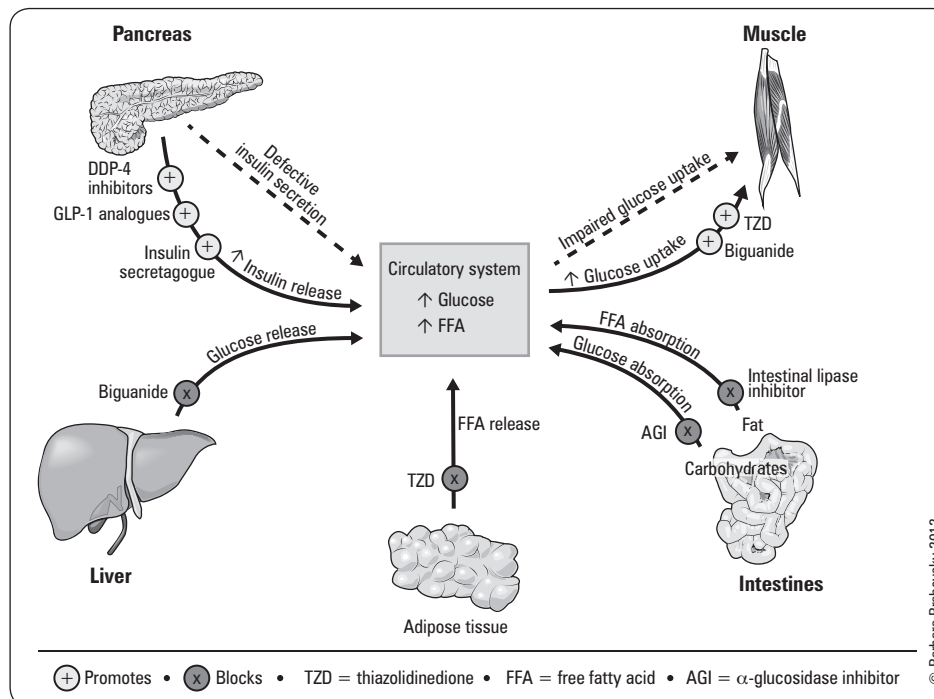
**Conclusion:** Treatment with simvastatin improved survival and cardiovascular outcomes in high-risk CAD patients.

**Table 6. Treatment of Hypercholesterolemia and Hypertriglyceridemia**

Treatment of Hypercholesterolemia	Treatment of Hypertriglyceridemia
<ul style="list-style-type: none"> <li>• <b>Conservative:</b> 4-6 mo trial unless high risk group, in which case medical treatment should start immediately               <ul style="list-style-type: none"> <li>• Diet                   <ul style="list-style-type: none"> <li>• Decrease fat: &lt;30% calories</li> <li>• Decrease saturated fat: &lt;10% calories</li> <li>• Decrease cholesterol: &lt;200 mg/d</li> <li>• Increase fibre: &gt;30 g/d</li> </ul> </li> <li>• Decrease alcohol intake to ≤1-2 drinks/d</li> <li>• Smoking cessation</li> <li>• Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</li> <li>• Weight loss: target body mass index (BMI) &lt;25</li> </ul> </li> <li>• <b>Medical</b> <ul style="list-style-type: none"> <li>• HMG-CoA reductase inhibitors, ezetimibe, bile acid sequestrants, niacin (see <i>Common Medications</i>, E52)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Conservative:</b> 4-6 mo trial               <ul style="list-style-type: none"> <li>• Diet                   <ul style="list-style-type: none"> <li>• Decrease fat and simple carbohydrates</li> <li>• Increase omega-3 polyunsaturated fatty acid</li> </ul> </li> <li>• Control blood sugars</li> <li>• Decrease alcohol intake to ≤1-2 drinks/d</li> <li>• Smoking cessation</li> <li>• Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</li> <li>• Weight loss: target body mass index (BMI) &lt;25</li> </ul> </li> <li>• <b>Medical:</b> fibrates, niacin (see <i>Common Medications</i>, E52)               <ul style="list-style-type: none"> <li>• Indications:                   <ul style="list-style-type: none"> <li>• Failed conservative measures</li> <li>• TG &gt;10 mmol/L (885 mg/dL) to prevent pancreatitis</li> </ul> </li> <li>• Combined hyperlipidemia</li> </ul> </li> </ul>

# Disorders of Glucose Metabolism

## Overview of Glucose Regulation



### Glucose Related Emergencies

- DKA
- HHS
- Hypoglycemia

Figure 3. Antihyperglycemic agents

## Pre-Diabetes (Impaired Glucose Tolerance/ Impaired Fasting Glucose)

- 1-5% per yr go on to develop diabetes mellitus
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance
- increased risk of developing macrovascular complications
- lifestyle modifications decrease progression to DM by 58%

### Diagnostic Criteria

- impaired fasting glucose (IFG): fasting blood glucose (FBG) 6.1-6.9 mmol/L (110-125 mg/dL)
- impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L (140-200 mg/dL)

## Diabetes Mellitus (DM)

### Definition

- syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/relative deficiency of insulin, or a reduction in biological effectiveness of insulin, or both

### Diagnostic Criteria

- any one of the following is diagnostic:
  - presence of classic symptoms of DM (polyuria, polydipsia, polyphagia, weight loss, blurry vision, nocturia, ketonuria) PLUS random blood glucose (BG)  $\geq 11.1$  mmol/L (200 mg/dL)
  - on at least two separate occasions:
    - ♦ FPG  $\geq 7.0$  mmol/L (126 mg/dL) (fasting = no caloric intake for at least 8 h) OR
    - ♦ 2h 75 g OGTT  $\geq 11.1$  mmol/L (200 mg/dL) OR
    - ♦ random PG  $\geq 11.1$  mmol/L (200 mg/dL) OR
    - ♦ HbA1c  $\geq 6.5\%$



In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1c, 2hPG in a 75 g OGTT) must be done on another day.



## Etiology and Pathophysiology

**Table 7. Etiologic Classification of Diabetes Mellitus**

<b>I. Type 1 diabetes</b> (immune-mediated $\beta$ cell destruction, usually leading to absolute insulin deficiency)
<b>II. Type 2 diabetes</b> (ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance 2° to $\beta$ cell dysfunction)
<b>III. Other specific causes of diabetes:</b> <ul style="list-style-type: none"> <li>a. Genetic defects of <math>\beta</math> cell function (e.g. MODY – Maturity-Onset Diabetes of the Young) or insulin action</li> <li>b. Diseases of the exocrine pancreas: <ul style="list-style-type: none"> <li>• Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis (“bronze diabetes”)</li> </ul> </li> <li>c. Endocrinopathies: <ul style="list-style-type: none"> <li>• Acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, hyperthyroidism</li> </ul> </li> <li>d. Drug-induced: <ul style="list-style-type: none"> <li>• Glucocorticoids, thyroid hormone, <math>\beta</math>-adrenergic agonists, thiazides, phenytoin, clozapine</li> </ul> </li> <li>e. Infections: <ul style="list-style-type: none"> <li>• Congenital rubella, CMV, coxsackie</li> </ul> </li> <li>f. Genetic syndromes associated with diabetes: <ul style="list-style-type: none"> <li>• Down’s syndrome, Klinefelter’s syndrome, Turner’s syndrome</li> </ul> </li> </ul>
<b>IV. Gestational Diabetes Mellitus</b> (see <a href="#">Obstetrics</a> , OB13)



**Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus**

	Type 1	Type 2
<b>Onset</b>	• Usually <30 yr of age	• Usually >40 yr of age • Increasing incidence in pediatric population 2° to obesity
<b>Epidemiology</b>	• More common in Caucasians • Less common in Asians, Hispanics, Aboriginals, and Blacks • Accounts for 5-10% of all DM	• More common in Blacks, Hispanics, Aboriginals, Asians • Accounts for >90% of all DM
<b>Etiology</b>	• Autoimmune	• Complex and multifactorial
<b>Genetics</b>	• Monozygotic twin concordance is 30-40% • Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of Type 1 DM • Certain DQ alleles also confer a risk	• Greater heritability than Type 1 DM • Monozygotic twin concordance is 70-90% • Polygenic • Non-HLA associated
<b>Pathophysiology</b>	• Synergistic effects of genetic, immune, and environmental factors that cause $\beta$ cell destruction resulting in impaired insulin secretion • Autoimmune process is believed to be triggered by environmental factors (e.g. viruses, bovine milk protein, urea compounds) • Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction • 80% of $\beta$ cell mass is destroyed before features of diabetes present	• Impaired insulin secretion, peripheral insulin resistance (likely due to receptor and post receptor abnormality), and excess hepatic glucose production
<b>Natural history</b>	<ul style="list-style-type: none"> <li>• After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin</li> <li>• Once these cells are destroyed, there is complete insulin deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Early on, glucose tolerance remains normal despite insulin resistance as <math>\beta</math> cells compensate with increased insulin production</li> <li>• As insulin resistance and compensatory hyperinsulinism continue, the <math>\beta</math> cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and diabetes</li> </ul>
<b>Circulating autoantibodies</b>	• Islet cell Ab present in up to 60-85% • Most common islet cell Ab is against glutamic acid decarboxylase (GAD) • Up to 60% have Ab against insulin	• <10%



### Three-year Efficacy of Complex Insulin Regimens in Type 2 Diabetes: 4T Trial *NEJM* 2009;361:1736-1747

**Study:** Randomized unblinded trial with 3 yr of follow-up.

**Population:** 708 patients with type 2 DM, not on insulin or thiazolidinedione therapy on maximal metformin and sulfonylurea therapy.

**Intervention:** Thrice-daily prandial insulin aspart, versus twice-daily biphasic insulin aspart, versus once-daily basal insulin detemir. Sulfonylurea therapy was replaced with a secondary insulin regime specific to each arm if there was persistent hyperglycemia.

**Primary Outcome:** 3-yr hemoglobin HbA1c.

**Results:** Significant difference in rates of patient withdrawal from the study: 5.1% biphasic, 11.7% prandial, 8.5% basal regimens ( $p=0.04$ ). There were no significant differences in median HbA1c levels between all three arms from yr 1 to 3. A smaller proportion of patients reached HbA1c <6.5% or <7.0% in the biphasic arm. The basal arm had least weight gain and least weight circumference increase, but highest rate of secondary insulin requirement. The basal arm had fewest severe hypoglycemic events per patient yr, while the biphasic had the most serious adverse effects.

**Conclusion:** Basal insulin regime provides the best glycemic control over a 3-yr study; with better HbA1c control, fewer hypoglycemic events, and less weight gain.



### Blood Glucose Control in Type 2 DM – UKPDS 33 *Lancet* 1998;352:837-853

**Study:** Randomized controlled trial (mean follow-up 10 yr).

**Patients:** 3867 patients with newly diagnosed Type 2 DM (mean age 53 yr, 61% men, 81% white, mean fasting plasma glucose (FPG) 6.1-15.0 mmol/L). Exclusions included severe cardiovascular disease, renal disease, retinopathy, and others.

**Intervention:** Intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <15 mmol/L without hyperglycemic symptoms).

**Main outcomes:** Diabetes-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia), diabetes-related death, and all-cause mortality.

**Results:** Patients allocated to intensive treatment had lower median HbA1c levels ( $p<0.001$ ).

Outcome	RRR % (p value)
Diabetes-related endpoint	12 (0.029)
Diabetes-related death	10 (0.34)
All-cause mortality	6 (0.44)

Patients allocated to intensive therapy had more hypoglycemic episodes and greater weight gain.

**Conclusion:** Intensive blood glucose control reduces microvascular, but not macrovascular complications in Type 2 DM.

**Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus** (continued)

	Type 1	Type 2
<b>Risk Factors</b>	<ul style="list-style-type: none"> <li>Personal history of other autoimmune diseases including Graves', myasthenia gravis, autoimmune thyroid disease, celiac disease and pernicious anemia</li> </ul>	<ul style="list-style-type: none"> <li>Age &gt;40 yr</li> <li>Abdominal obesity/overweight</li> <li>First-degree relative with DM</li> <li>Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander)</li> <li>Hx of IGT or IFG</li> <li>HTN</li> <li>Dyslipidemia</li> <li>PCOS</li> <li>Hx of gestational DM or macrosomic baby</li> <li>Schizophrenia</li> <li>Fatty liver</li> <li>Hyperuricemia</li> </ul>
<b>Body Habitus</b>	<ul style="list-style-type: none"> <li>Normal to thin</li> </ul>	<ul style="list-style-type: none"> <li>Typically overweight with increased central obesity</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>Insulin</li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle modification</li> <li>Oral antihyperglycemic agents</li> <li>Incretin therapy</li> <li>Insulin therapy</li> </ul>
<b>Acute Complication</b>	<ul style="list-style-type: none"> <li>Diabetic ketoacidosis (DKA) in severe cases</li> </ul>	<ul style="list-style-type: none"> <li>Hyperosmolar hyperglycemic state (HHS)</li> <li>DKA in severe cases</li> </ul>
<b>Screening</b>	<ul style="list-style-type: none"> <li>Subclinical prodrome can be detected in first and second-degree relatives of those with Type 1 DM by the presence of pancreatic islet autoantibodies</li> </ul>	<ul style="list-style-type: none"> <li>Screen individuals with risk factors</li> </ul>



#### Targeting Intensive Glycemic Control versus Targeting Conventional Glycemic Control for Type 2 Diabetes Mellitus

*Cochrane DB Syst Rev* 2011;6:CD008143

**Study:** Systematic review of randomized clinical trials of glycemic control in adults with T2DM.

**Patients:** Twenty trials randomized 16,106 patients with Type 2 DM to intensive control and 13,880 patients with Type 2 DM to conventional glycemic control.

**Intervention:** Intensive glycemic control (HbA1c ≤6.5%) versus conventional glycemic control (determined by local guidelines).

**Primary Outcomes:** All-cause mortality, composite macrovascular (death from cardiovascular cause, nonfatal MI, nonfatal stroke) and microvascular events (nephropathy, retinopathy).

**Results:** There was no significant difference between targeting intensive and conventional glycemic control for all-cause mortality or cardiovascular mortality. Targeting intensive glycemic control reduced the risk of amputation, the composite risk of microvascular disease, retinopathy, retinal photocoagulation, and nephropathy. The risks of both mild and severe hypoglycemia were increased with targeting intensive glycemic control.

**Conclusions:** Intensive glycemic control did not reduce all-cause mortality and cardiovascular mortality compared to conventional glycemic control. Intensive glycemic control reduced the risk of microvascular complications while increasing the risk of hypoglycemia. Intensive glycemic control may also reduce the risk of non-fatal MI in trials exclusively dealing with glycemic control in usual care settings.



#### Canadian Diabetes Guidelines 2013

	Target
HbA1c	<7.0%
Fasting plasma glucose	4-7 mmol/L (72-126 mg/dL)
2h post prandial glucose	5-10 mmol/L (90-180 mg/dL)
	5-8 mmol/L (90-144 mg/dL) if not meeting target A1c and can be safely achieved
Lipids	As per high risk group if age >40 or age >30 if diabetes duration >15 yr
Blood pressure	<130/80

## Treatment of Diabetes

### Glycemic Targets

- HbA1c reflects glycemic control over 3 mo and is a measure of patient's long-term diabetes control
- therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications
- more intensive glucose control, HbA1c <6.5%, may be targeted in patients with a shorter duration of diabetes with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia
- a HbA1c target <8.5% may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple co-morbidities, extensive CAD, and a failure to attain established glucose targets despite treatment intensification
- there may be harm associated with strategy to target HbA1c <6.0% in certain patients with Type 2 DM (see ACCORD trial, E9)

### Diet

- daily carbohydrate intake 45-60% of energy, protein 15-20% of energy and fat <35% of energy
- intake of saturated fats <7% and polyunsaturated fats <10% of total calories each
- limit sodium, alcohol and caffeine intake
- Type 1: carbohydrate counting is used to titrate insulin regimen
- Type 2: weight reduction

### Lifestyle

- regular physical exercise to improve insulin sensitivity, lower lipid concentrations and control blood pressure
- smoking cessation

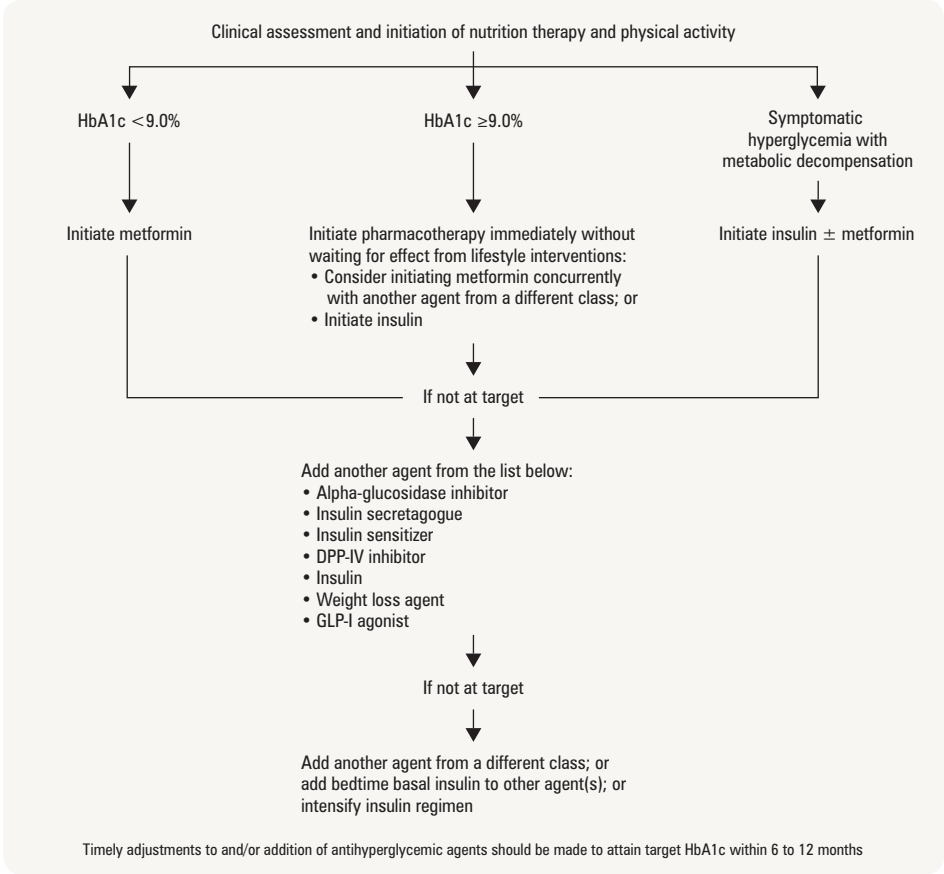
### Medical Treatment: Oral Antihyperglycemic Agents and/or Incretin Therapy (Type 2 DM)

- initiate oral antihyperglycemic therapy and/or incretin therapy within 2-3 mo if lifestyle management does not result in glycemic control
- if HbA1c >9.0%, initiate pharmacologic therapy immediately and consider combination oral therapy or insulin immediately
- see *Common Medications*, E52 for details on antihyperglycemic agents

### Medical Treatment: Insulin (Figure 5)

- used for Type 1 DM at onset, may be used in Type 2 DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- bolus insulins: short-acting (Insulin regular), rapid-acting analogue (Insulin aspart, Insulin lispro, Insulin glulisine)

- basal insulins: intermediate-acting (Insulin NPH), long-acting analogue (Insulin detemir, Insulin glargine)
- premixed insulins (% Humulin R and % NPH) 30/70; premixed insulin analogues (Biphasic Insulin aspart, Insulin lispro/lispro protamine)
- estimated total daily insulin requirement: 0.5-0.7 units/kg (often start with 0.3-0.5 units/kg/day)



**Figure 4. Approach to treatment of hyperglycemia in type 2 DM**  
Adapted from: Can J Diabetes 2008;32(suppl1):S56

**Table 9. Available Insulin Formulations**

Insulin Type (trade name)	Onset	Peak	Duration
PRANDIAL (BOLUS) INSULINS			
Rapid-acting insulin analogues			
• Insulin aspart (NovoRapid®)	10-15 min	1-1.5 h	3-5 h
• Insulin lispro (Humalog®)	10-15 min	1-2 h	3.5-4.75 h
• Insulin glulisine (Apidra®)	10-15 min	1-1.5 h	3-5 h
Short-acting insulins			
• Humulin R®	30 min	2-3 h	6.5 h
• Novolin Toronto®			
BASAL INSULINS			
Intermediate-acting			
• Humulin N®	1-3 h	5-8 h	Up to 18 h
• Novolin NPH®			
Long-acting basal insulin analogues			
Insulin detemir (Levemir®)	90 min	Not applicable	Up to 24 h (glargine 24 h, detemir 16-24 h)
Insulin glargine (Lantus®)			
PRE-MIXED INSULINS			
Premixed regular insulin – NPH			
• Humulin 30/70®	A single vial or cartridge contains a fixed ratio of insulin (% of rapid acting or short-acting insulin to % of intermediate-acting insulin)		
• Novolin 30/70®			
Premixed insulin analogues			
• Biphasic insulin aspart (NovoMix 30®)			
• Insulin lispro/lispro protamine (Humalog Mix25® and Mix50®)			



**Effects of Intensive Glucose Lowering in Type 2 DM: The ACCORD Trial**

*NEJM* 2008;358:2545-2559  
**Study:** Multicentre RCT.  
**Patients:** 10,251 patients (mean age 62.2) with Type 2 DM, and cardiovascular risk factors.  
**Intervention:** Intensive therapy targeting a HbA1c level of less than 6.0% or standard therapy targeting 7.0 to 7.9%.  
**Outcomes:** First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.  
**Results:** The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV-cause mortality, nonfatal MI, and all congestive heart failure in the intensive therapy group. There were increased rates of all hypoglycemic events, any nonhypoglycemic serious adverse event, fluid retention, and weight gain > 10 kg, but lower systolic and diastolic blood pressure in the intensive therapy group. There was an increased incidence of elevated ALT (>3 times upper limit) and ACE drug use in the standard therapy group.  
**Conclusions:** Intensive glucose lowering therapy in Type 2 DM does not improve clinic outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy. Additional research is required to discern the cause.



**Effects of Intensive Blood Pressure Control in Type 2 DM: The ACCORD Trial**

*NEJM* 2010;362:1575-1585  
**Study:** RCT, unblinded with 4.7 yr of mean follow-up.  
**Population:** 4,733 patients with type 2 DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg.  
**Intervention:** sBP control less than 120 mmHg (intensive) or 140 mmHg (standard).  
**Primary Outcomes:** Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death).  
**Results:** Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI, 3.4-3.5) versus 2.1 (95%, 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.27%, p=<0.001); especially bradycardia or arrhythmia (0.5% vs. 0.13%, p=0.02) and hyperkalemia (0.4% vs. 0.04%, p=0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32%/yr vs. 0.53%/yr, p=0.01) and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, p=0.03) in the intensive therapy arm.  
**Conclusions:** Intensive BP lowering to less than 120 mmHg versus 140 mmHg in patients with Type 2 DM and CV risk factors does not reduce major CV event risk reduction except for stroke events.



**Effects of Combination Lipid Therapy in Type 2 DM: the ACCORD Trial**

*NEJM* 2010;362:1563-1574  
**Study:** RCT, double-blinded trial with 4.7 yr of mean follow-up.  
**Population:** 5,518 patients with type 2 DM.  
**Intervention:** Statin with or without fibrate therapy.  
**Primary Outcome:** Major cardiovascular (CV) event (composite nonfatal MI, nonfatal stroke, or CV-related death).  
**Results:** No significant differences in primary outcome between the two arms. No difference in all MI, all stroke, or all-cause mortality between study arms.  
**Conclusions:** The addition of fibrate therapy to statin therapy in patients with Type 2 DM does not reduce major CV event risk.

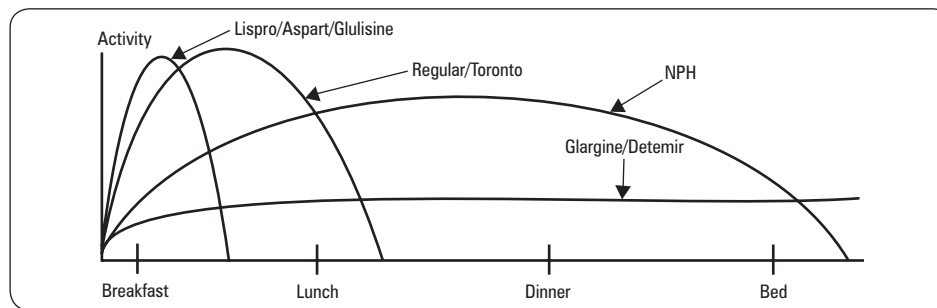


Figure 5. Duration of activity of different insulins

## Insulin Regimens

Table 10. Insulin Regimens for T2DM and T1DM

Regimen	Administration
T2DM Oral hypoglycemic agent + basal insulin	<ul style="list-style-type: none"> <li>Start with 10 units at bedtime of basal insulin</li> <li>Titrate up by 1 unit until FBG &lt;7.0 mmol/L (126 mg/dL)</li> </ul>
T1DM Multiple daily injections (MDI)	<ul style="list-style-type: none"> <li>Estimated total insulin requirement is 0.5-0.7 U/kg</li> <li>40% is given as basal insulin at bedtime</li> <li>20% is given as bolus insulin before breakfast, lunch and dinner</li> <li>Continue metformin but discontinue secretagogue</li> </ul>
Split-mixed	<ul style="list-style-type: none"> <li>Estimated total insulin requirement is 0.5-0.7 U/kg</li> <li>2/3 dose is given as pre-mixed insulin before breakfast</li> <li>1/3 dose is given as pre-mixed insulin before dinner</li> <li>Continue metformin but discontinue secretagogue</li> </ul>

\*Bolus insulin: Aspart, Glulisine, Lispro

\*Basal insulin: Glargine, Detemir, NPH

\*Pre-mixed insulin: Humulin 30/70, Novolin 30/70, Novomix 30, Humalog Mix25, Humalog Mix50

Table 11. Titrating Insulin Doses

Hyperglycemic Reading	Insulin Correction
High AM sugar	Increase bedtime basal insulin
High lunch sugar	Increase AM rapid/regular insulin
High supper sugar	Increase lunch rapid/regular insulin, or Increase AM basal insulin
High bedtime sugar	Increase supper rapid/regular insulin

## Variable Insulin Dose Schedule ("Sliding/Supplemental/Correction Scale")

- for patients on Basal-Bolus MDI regimen: patient takes usual doses of basal insulin but varies doses of bolus insulin based on BG reading at time of dose
- use baseline bolus insulin dose when within BG target range; add or subtract units when above or below target
- when used in hospital (including perioperative management of diabetes) patient should also receive basal insulin to prevent fluctuations in blood sugar levels or long periods of hyperglycemia without intervention
- construction of a supplemental sliding scale for a patient on anti-hyperglycemics:
  - Correction Factor (CF) =  $100/\text{Total Daily Dose of insulin (TDD)}$
  - BG <4: call MD and give 15 g carbohydrates
  - BG between 4 to 8: no additional insulin
  - BG between 8 to (8 + CF): give one additional unit
  - BG between (8 + CF) to (8 + 2CF): give two additional units
  - BG between (8 + 2CF) to (8 + 3CF): give three additional units

## Insulin Pump Therapy [continuous subcutaneous insulin infusion (CSII)]

- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected



### DPP-IV Inhibitors

- Newer antihyperglycemic agents (e.g. sitagliptin, saxagliptin) that inhibit the degradation of endogenous incretin hormones like GLP-1
- Stimulate insulin secretion, inhibit glucagon release from the pancreas

### GLP-1 Analogues (Incretins)

- Human glucagon-like peptide-1 analogues: exenatide, liraglutide
- Increase insulin secretion, decreases inappropriate glucagon secretion, increases B-cell growth/replication, slows gastric emptying and decreases food intake
- Associated with weight loss
- Subcutaneous formulation



### Treatment of DKA/HHS

- Fluids
- Insulin
- Potassium
- Search for and treat precipitant



### Conversion Chart for percentage HbA1c to average blood sugar control

Average blood sugar level (mmol/L)	Hemoglobin A1c (% HbA1c)
17	12%
16	11%
14	10%
12	9%
10	8%
8	7%
6	6%

Conversion chart adapted from Nathan DM *et al.* The clinical information value of a glycosylated hemoglobin assay. *NEJM* 1984;310:341-346



### The 8 Is Precipitating DKA:

- Infection
- Ischemia or Infarction
- Iatrogenic (glucocorticoids)
- Intoxication
- Insulin missed
- Initial presentation
- Intra-abdominal process (e.g. pancreatitis, cholecystitis)
- Intraop/periop stress

## Acute Complications

**Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States**

	Diabetic Ketoacidosis (DKA)	Hyperosmolar Hyperglycemic State (HHS)
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>Usually occurs in Type 1 DM</li> <li>Insulin deficiency with ↑ counterregulatory hormones (glucagon, cortisol, catecholamines, GH)</li> <li>Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise)</li> <li>Unrestricted hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na<sup>+</sup> (water shift to ECF)</li> <li>Fat mobilization → ↑ FFA → ketoacids → metabolic acidosis</li> <li>Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria</li> <li>Total body K<sup>+</sup> depletion but serum K<sup>+</sup> may be normal or elevated 2° to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality</li> <li>Total body PO<sub>4</sub><sup>3-</sup> depletion</li> </ul>	<ul style="list-style-type: none"> <li>Occurs in Type 2 DM</li> <li>Often precipitated by sepsis, stroke, MI, CHF, renal failure, trauma, drugs (glucocorticoids, immunosuppressants, phenytoin, diuretics), dialysis, recent surgery, burns</li> <li>Partial or relative insulin deficiency decreases glucose utilization in muscle, fat, and liver while inducing hyperglucagonemia and hepatic glucose production</li> <li>Presence of a small amount of insulin prevents the development of ketosis by inhibiting lipolysis</li> <li>Characterized by hyperglycemia, hyperosmolality, and dehydration without ketosis</li> <li>More severe dehydration compared to DKA due to more gradual onset and ↑ duration of metabolic decompensation plus impaired fluid intake which is common in bedridden or elderly</li> <li>Volume contraction → renal insufficiency → ↑ hyperglycemia, ↑ osmolality → shift of fluid from neurons to ECF → mental obtundation and coma</li> </ul>
<b>Clinical Features</b>	<ul style="list-style-type: none"> <li>Polyuria, polydipsia, polyphagia with marked fatigue, nausea, vomiting</li> <li>Dehydration (orthostatic changes)</li> <li>LOC may be ↓ with ketoacidosis or with high serum osmolality (osm &gt; 330 mmol/L)</li> <li>Abdominal pain</li> <li>Fruity smelling breath</li> <li>Kussmaul's respiration</li> </ul>	<ul style="list-style-type: none"> <li>Onset is insidious → preceded by weakness, polyuria, polydipsia</li> <li>History of decreased fluid intake</li> <li>History of ingesting large amounts of glucose containing fluids</li> <li>Dehydration (orthostatic changes)</li> <li>↓ LOC → lethargy, confusion, comatose due to high serum osmolality</li> <li>Kussmaul's respiration is absent unless the underlying precipitant has also caused a metabolic acidosis</li> </ul>
<b>Serum</b>	<ul style="list-style-type: none"> <li>↑ BG (typically 11-55 mmol/L, 198-990 mg/dL), ↓ Na<sup>+</sup> (2° to hyperglycemia → for every ↑ in BG by 10 mmol/L (180 mg/dL) there is a ↓ in Na<sup>+</sup> by 3 mmol/L)</li> <li>Normal or ↑ K<sup>+</sup>, ↓ HCO<sub>3</sub><sup>-</sup>, ↑ BUN, ↑ Cr, ketonemia, ↓ PO<sub>4</sub><sup>3-</sup></li> <li>↑ osmolality</li> </ul>	<ul style="list-style-type: none"> <li>↑ BG (typically 44.4-133.2 mmol/L, 800-2400 mg/dL)</li> <li>In mild dehydration, may have hyponatremia (spurious 2° to hyperglycemia → for every ↑ in BG by 10 mmol/L (180 mg/dL) there is a ↓ in Na<sup>+</sup> by 3 mmol/L) – if dehydration progresses, may get hypernatremia</li> <li>Ketosis usually absent or mild if starvation occurs</li> <li>↑ osmolality</li> </ul>
<b>ABG</b>	<ul style="list-style-type: none"> <li>Metabolic acidosis with ↑ AG, possible 2° respiratory alkalosis</li> <li>If severe vomiting/dehydration there may be a metabolic alkalosis</li> </ul>	<ul style="list-style-type: none"> <li>Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI)</li> </ul>
<b>Urine</b>	<ul style="list-style-type: none"> <li>+ve for glucose and ketones</li> </ul>	<ul style="list-style-type: none"> <li>-ve for ketones unless there is starvation ketosis</li> <li>Glycosuria</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>Immediate resuscitation and emergency measures if patient is stuporous or comatose</li> <li>Monitor degree of ketoacidosis with AG, not BG or serum ketone level</li> <li>Rehydration:               <ul style="list-style-type: none"> <li>1 L/h NS in first 2 h</li> <li>after 1st 2 L, 300-400 mL/h 0.45% NaCl (continue NS if corrected sodium is falling faster than 3 mosm/kg water/h)</li> <li>once BG reaches 13.9 mmol/L (250 mg/dL) then switch to D5W to maintain BG in the range of 13.9–16.6 mmol/L (250-300 mg/dL)</li> </ul> </li> <li>Insulin therapy:               <ul style="list-style-type: none"> <li>critical to resolve acidosis, not hyperglycemia</li> <li>do not use with hypokalemia (see below), until serum K<sup>+</sup> is corrected to &gt; 3.3 mmol/L</li> <li>use only regular insulin (R)</li> <li>maintain on 0.1 U/kg/h insulin R infusion</li> <li>check serum glucose hourly</li> </ul> </li> <li>K<sup>+</sup> replacement:               <ul style="list-style-type: none"> <li>with insulin administration, hypokalemia may develop</li> <li>if serum K<sup>+</sup> &lt; 3.3 mmol/L, hold insulin and give 40 mEq/L K<sup>+</sup> replacement</li> <li>when K<sup>+</sup> 3.5-5.0 mmol/L add KCl 20-40 mEq/L IV fluid to keep K<sup>+</sup> in the range of 3.5-5 mEq/L</li> </ul> </li> <li>HCO<sub>3</sub><sup>-</sup>:               <ul style="list-style-type: none"> <li>if pH &lt; 7.0 or if hypotension, arrhythmia or coma is present with a pH of &lt; 7.1 give HCO<sub>3</sub><sup>-</sup> in 0.45% NaCl</li> <li>do not give if pH &gt; 7.1 (risk of metabolic alkalosis!)</li> <li>can give in case of life-threatening hyperkalemia</li> </ul> </li> <li>± mannitol (for cerebral edema)</li> </ul>	<ul style="list-style-type: none"> <li>Same resuscitation and emergency measures as DKA</li> <li>Rehydration:               <ul style="list-style-type: none"> <li>IV fluids: 1 L/h NS initially</li> <li>evaluate corrected serum Na<sup>+</sup></li> <li>if corrected serum Na<sup>+</sup> high or normal, switch to 0.45% NaCl (4-14 mL/kg/h)</li> <li>if corrected serum Na<sup>+</sup> low, maintain NS (4-14 mL/kg/h)</li> <li>when serum BG reaches 13.9 mmol/L (250 mg/dL) switch to D5W</li> </ul> </li> <li>K<sup>+</sup> replacement:               <ul style="list-style-type: none"> <li>less severe K<sup>+</sup> depletion compared to DKA</li> <li>if serum K<sup>+</sup> &lt; 3.3 mmol/L, hold insulin and give 40 mEq/L K<sup>+</sup> replacement</li> <li>if K<sup>+</sup> is 3.3-5.0, give KCl 20-30 mEq/L IV fluid</li> <li>if serum K<sup>+</sup> ≥ 5.5 mmol/L, check K<sup>+</sup> every 2 h</li> </ul> </li> <li>Search for precipitating event</li> <li>Insulin therapy:               <ul style="list-style-type: none"> <li>use only regular insulin (R)</li> <li>initially load 0.1 U/kg body weight insulin R bolus</li> <li>maintenance 0.1 U/kg/h insulin R infusion or IM</li> <li>check serum glucose hourly</li> <li>in general lower insulin requirement compared to DKA</li> </ul> </li> </ul>
<b>Prognosis</b>	<ul style="list-style-type: none"> <li>2-5% mortality in developed countries</li> <li>Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children)</li> </ul>	<ul style="list-style-type: none"> <li>Overall mortality approaches 50% primarily because of the older patient population and underlying etiology/precipitant</li> </ul>



## Macrovascular Complications

- increased risk of coronary artery disease (CAD), ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- coronary artery disease (see [Cardiology, C22](#))
  - risk of MI is 3-5x higher in those with diabetes compared to age-matched controls
  - CAD is the leading cause of death in Type 2 DM
  - most patients with DM are considered “high risk” under the risk stratification for CAD (see *Dyslipidemias, E2*)
- ischemic stroke (see [Neurology, N43](#))
  - risk of stroke is approximately 2.5x higher in those with diabetes
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - HbA1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see [Cardiology, C44](#))
  - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with diabetes compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with diabetes
- treatment
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight low density lipoprotein (LDL) cholesterol control [LDL <2.0 mmol/L (77 mg/dL)]
  - ACE inhibitor or angiotensin receptor blocker in high-risk patients
  - smoking cessation



### All Ketonemia is not DKA:

Consider starvation or alcohol ketosis.



Average fluid loss runs at 3-6 L in DKA, and 8-10 L in HHS.



### Laboratory Testing: Ketones

The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect  $\beta$ -hydroxybutyrate (BHB), the ketone most frequently in excess. This has two clinical consequences:

- Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives because of the presence of BHB.
- As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening when in fact they are improving.

## Microvascular Complications

### DIABETIC RETINOPATHY (see [Ophthalmology, OP35](#))



#### Epidemiology

- Type 1 DM: 25% affected at 5 yr, 100% at 20 yr
- Type 2 DM: 25% affected at diagnosis, 60% at 20 yr
- leading cause of blindness in North America between the ages of 20-74
- most important factor is disease duration

#### Clinical Features

- nonproliferative
  - asymptomatic but if macular involvement occurs vision may be impaired
  - microaneurysms, hard exudates, dot-blot and flame hemorrhages
- preproliferative
  - macular edema, cotton wool spots, venous shunts and beading, intra-retinal microvascular abnormalities (IRMA)
- proliferative
  - with neovascularization and fibrous scarring; great risk for loss of vision secondary to vitreous hemorrhage (floaters) and/or retinal detachment

#### Treatment and Prevention

- tight glycemic control (delays onset, decreases progression), tight lipid control, manage hypertension, smoking cessation
- pan-retinal laser photocoagulation for treatment of neovascularization
- vitrectomy
- annual follow-up visits with an optometrist or ophthalmologist examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of Type 2 DM; 5 yr after diagnosis of Type 1 DM)
- interval for follow-up should be tailored to severity of retinopathy



### Effect of a Multifactorial Intervention on Mortality in Type 2 DM: The Steno-2 Study

NEJM 2008;358:580-591

**Study:** Single centre RCT.

**Patients:** Patients (n=160) with Type 2 DM and persistent microalbuminuria.

**Intervention:** Random assignment to receive either conventional multifactorial treatment or intensified, target-driven therapy involving a combination of medications and focused behaviour modification. Targets included an HbA1c level of <6.5%, a fasting serum total cholesterol level of <4.5 mmol/L, a fasting serum triglyceride level of <1.7 mmol/L, a sBP of <130 mmHg, and a dBP of <80 mmHg. Patients were treated with blockers of the renin-angiotensin system because of their microalbuminuria, regardless of blood pressure, and received low-dose Aspirin® as primary prevention.

**Outcomes:** The primary end point was the time to death from any cause. Other endpoints examined were death from CV causes and various CV events along with diabetic neuropathy, nephropathy, and retinopathy.

**Results:** Twenty-four patients in the intensive-therapy group died, as compared with 40 in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI], 0.32 to 0.89; p=0.02). Intensive therapy was associated with a lower risk of death from CV causes (hazard ratio, 0.43; 95% CI, 0.19 to 0.94; p=0.04) and of CV events (hazard ratio, 0.41; 95% CI, 0.25 to 0.67; p<0.001). One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with six patients in the conventional-therapy group (p=0.04). Fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI, 0.23 to 0.86; p=0.02).

**Conclusions:** In at-risk patients with Type 2 DM, intensive intervention with multiple drug combinations and behaviour modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from CV causes.



**DIABETIC NEPHROPATHY** (see [Nephrology](#), NP28)**Epidemiology**

- diabetes-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with Type 1 DM (after 5-10 yr) and 4-20% with Type 2 DM have progressive nephropathy

**Pathophysiology**

- thickening of capillary basement membrane and glomerular mesangium resulting in glomerulosclerosis and renal insufficiency
- diffuse glomerulosclerosis is more common than nodular intercapillary glomerulosclerosis (Kimmelstiel-Wilson lesions)

**Screening**

- serum creatinine
- random urine test for albumin to creatinine ratio (ACR) plus urine dipstick test for all Type 2 DM patients at diagnosis, then annually, and for postpubertal Type 1 DM patients with  $\geq 5$  yr duration of DM

**Clinical Features**

- initial changes include microalbuminuria, increased GFR (up to 140%) from hyperfiltration, enlarged kidneys
- microalbuminuria: ACR of  $>2.0$  mg/mmol (men) or  $>2.8$  mg/mmol (women)
- macroalbuminuria: ACR of  $>20.0$  mg/mmol (men) or  $>28.0$  mg/mmol (women)
- progression over 15 yr to cause hypertension, persistent proteinuria (macroalbuminuria), nephrotic syndrome, and renal failure
- elevated HbA1c is an independent risk factor for progression to microalbuminuria

**Treatment and Prevention**

- tight glycemic control
- tight blood pressure control ( $<130/80$  mmHg): can use either ACEI or ARB (often used first line for their CVD protection)
- even in the absence of glycemic control ACEIs or ARBs reduce the level of albuminuria and the rate of progression of renal disease in normotensive and hypertensive patients with Type 1 or Type 2 DM
- Type 1 DM  $\rightarrow$  CKD with either hypertension or albuminuria  $\rightarrow$  ACEIs 1st line; ARBs 2nd line
- Type 2 DM  $\rightarrow$  CKD with hypertension and albuminuria  $\rightarrow$  ACEIs or ARBs (dose adjust if creatinine clearance (CrCl)  $<60$  mL/min)
- consider use of non-dihydropyridine calcium channel blocker (e.g. diltiazem) in those unable to tolerate both ACEIs and ARBs
- limit use of nephrotoxic drugs and dyes
- renal failure may necessitate hemodialysis and renal transplant

**DIABETIC NEUROPATHY** (see [Neurology](#), N37)**Epidemiology**

- approximately 50% of patients within 10 yr of onset of Type 1 DM and Type 2 DM

**Pathophysiology**

- can have peripheral sensory neuropathy, motor neuropathy or autonomic neuropathy
- mechanism poorly understood
- acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerve
- the more common motor and sensory neuropathies are thought to be related to metabolic or osmotic toxicity secondary to increased sorbitol and/or decreased myoinositol (possible mechanisms include accumulation of advanced glycation endproducts [AGE], oxidative stress, protein kinase C, nerve growth factor deficiency)

**Screening**

- 128 Hz tuning fork or 10 g monofilament at diagnosis and annually in people with Type 2 DM and after 5 yr duration of Type 1 DM

**Management of Diabetic Retinopathy: A Systematic Review**

JAMA 2007;298:902-916

**Purpose:** To review the best evidence for primary and secondary interventions in the management of diabetic retinopathy (DR), including diabetic macular edema.

**Study Selection:** English-language RCTs with more than 12 mo of follow-up and meta-analyses were included.

**Results:** Forty-four studies (including 3 meta-analyses) met the inclusion criteria. Tight glycemic and blood pressure control reduces the incidence and progression of DR. Pan-retinal laser photocoagulation reduces the risk of moderate and severe visual loss by 50% in patients with severe nonproliferative and proliferative retinopathy. Focal laser photocoagulation reduces the risk of moderate visual loss by 50 to 70% in eyes with macular edema. Early vitrectomy improves visual recovery in patients with proliferative retinopathy and severe vitreous hemorrhage. Intravitreal injections of steroids may be considered in eyes with persistent loss of vision when conventional treatment has failed.

**Conclusions:** Tight glycemic and blood pressure control remains the cornerstone in the primary prevention of DR. Pan-retinal and focal retinal laser photocoagulation reduces the risk of visual loss in patients with severe DR and macular edema, respectively. There is currently insufficient evidence to recommend routine use of other treatments.



## Clinical Features

**Table 13. Clinical Presentation of Diabetic Neuropathies**

Peripheral Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation	Less common than sensory neuropathy	Postural hypotension, tachycardia, decreased cardiovascular response to Valsalva maneuver
Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands	Delayed motor nerve conduction and muscle weakness/atrophy	Gastroparesis and alternating diarrhea and constipation
Decreased ankle reflex	May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex)	Urinary retention and erectile dysfunction
Symptoms may first occur in entrapment syndromes e.g. carpal tunnel	Some of the motor neuropathies spontaneously resolve after 6-8 wk	
May result in neuropathic ulceration of foot	Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell's palsy)	
	Diabetic amyotrophy: refers to pain, weakness, and wasting of hip flexors or extensors	

## Treatment and Management

- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anti-epileptics (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), erythromycin (stimulates motilin receptors)
- medical, mechanical and surgical treatment for erectile dysfunction (see [Urology](#), U30)



### Effects of Treatments for Symptoms of Painful Diabetic Neuropathy: Systematic Review

BMJ 2007;335:87

**Purpose:** To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.

**Study Selection:** RCTs comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.

**Results:** 25 included reports compared anticonvulsants (n=1270), antidepressants (94), opioids (329), ion channel blockers (173), NMDA antagonist (14), duloxetine (805), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% confidence interval 1.77 to 16.02) for traditional anticonvulsants, 3.25 (2.27 to 4.66) for newer generation anticonvulsants, and 22.24 (5.83 to 84.75) for tricyclic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (0.33 to 6.96) for traditional anticonvulsants, 2.98 (1.75 to 5.07) for newer generation anticonvulsants, and 2.32 (0.59 to 9.69) for tricyclic antidepressants.

**Conclusion:** Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer anticonvulsants. Evidence of the long term effects of antidepressants and anticonvulsants is lacking. Further studies are needed on opioids, NMDA antagonists, and ion channel blockers.

## Other Complications

### Dermatologic

- diabetic dermopathy: atrophic brown spots commonly in pretibial region known as “shin spots”, secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipoidica diabetorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

### Bone and Joint Disease

- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren's contracture
- bone demineralization: bone density 10-20% below normal
- frozen shoulder

### Cataracts

- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

### Infections

- see [Infectious Diseases](#), ID16

## Hypoglycemia

### Etiology and Pathophysiology

- hypoglycemia occurs most frequently in people with diabetes receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without diabetes, care must be taken to distinguish fasting from post-prandial hypoglycemia as each invokes separate differential diagnoses



### Other Players in Glucose Homeostasis

These hormones act to increase blood glucose levels

- Glucagon
- Epinephrine
- Cortisol
- Growth hormone



### C-Peptide

A short peptide released into the circulation when proinsulin is cleaved to insulin.

**Table 14. Common Causes of Hypoglycemia**

Fasting		Post-Prandial (Nonfasting, Reactive)
Hyperinsulinism	Without Hyperinsulinism	
<ul style="list-style-type: none"> <li>Exogenous insulin</li> <li>Sulfonylurea or meglitinide reaction</li> <li>Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor)</li> <li>Pentamidine</li> <li>Pancreatic <math>\beta</math> cell tumour – insulinoma</li> </ul>	<ul style="list-style-type: none"> <li>Severe hepatic dysfunction</li> <li>Chronic renal insufficiency</li> <li>Hypocortisolism</li> <li>Alcohol use</li> <li>Non-pancreatic tumours</li> <li>Inborn error of carbohydrate metabolism, glycogen storage disease, gluconeogenic enzyme deficiency</li> </ul>	<ul style="list-style-type: none"> <li>Alimentary</li> <li>Functional</li> <li>Noninsulinoma pancreatogenous hypoglycemic syndrome</li> <li>Occult diabetes</li> <li>Leucine sensitivity</li> <li>Hereditary fructose intolerance</li> <li>Galactosemia</li> <li>Newborn infant of diabetic mother</li> </ul>

**Clinical Features**

- Whipple's triad
  - serum glucose  $<2.5$  mmol/L (45 mg/dL) in males and  $<2.2$  mmol/L (40 mg/dL) in females
  - neuroglycopenic symptoms
  - rapid relief provided by administration of glucose
- adrenergic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia
- neuroglycopenic symptoms (caused by decreased activity of CNS)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

**Investigations**

- electrolytes, creatinine, LFTs, drugs/toxins, cortisol
- if concerned about possible insulinoma:
  - bloodwork to be drawn when patient is hypoglycemic (e.g. during hospitalized 72-h fast) for glucose, serum ketones, insulin, pro-insulin, C-peptide, insulin antibodies

**Treatment**

- for fasting hypoglycemia, must treat underlying cause
- for post-prandial (reactive) hypoglycemia, frequent small feeds
- see [Emergency Medicine](#), ER36
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV or 1 mg glucagon SC (if no IV available)
  - may need ongoing glucose infusion once BG  $>5$  mmol/L (90 mg/dL)



**Use C-peptide Levels to Distinguish between Exogenous and Endogenous Source of Hyperinsulinemia**  
 Increased = endogenous  
 Decreased or normal = exogenous



**Treatment of Acute Hypoglycemic Episode (Blood Glucose  $<4.0$  mmol/L) in the Awake Patient (e.g. able to self-treat)**

- 1) Eat 15 g of carbohydrates (CHO) (e.g. 3 packets sugar dissolved in water; 3/4 cup of juice)
- 2) Wait 15 min
- 3) Retest Blood Glucose (BG)
- 4) Repeat steps 1-3 until BG  $>5$  mmol/L
- 5) Eat next scheduled meal. If next meal is  $>1$  h away, eat snack including 15 g of CHO and protein.



**Hypoglycemia Unawareness: (Type 1 DM  $>>>$  Type 2 DM)**

Patient remains asymptomatic until severely hypoglycemic levels are reached

**Causes:**

- Decreased glucagon/epinephrine response
- History of repeated hypoglycemia or low HbA1c
- Autonomic neuropathy
- Not safe to drive



Suggest that patient obtain a Medic-Alert bracelet if at risk for hypoglycemia, especially with hypoglycemia unawareness.

**Features of Metabolic Syndrome**

Risk Factor	IDF (2005): to make diagnosis requires abdominal obesity + $\geq 2$ additional risk factors	ATP III (2005): requires $\geq 3$ risk factors
-------------	---	--

<b>Abdominal Obesity</b>		
Men	WC $\geq 94$ cm (37 inches)	WC $\geq 102$ cm (40 inches)
Women	WC $\geq 80$ cm (31.5 inches)	WC $\geq 88$ cm (35 inches)
<b>Triglyceride Level</b>		
	$\geq 1.7$ mmol/L (150 mg/dL)	$\geq 1.7$ mmol/L (150 mg/dL)
<b>HDL-C Level</b>		
Men	$<1.0$ mmol/L ( $<40$ mg/dL)	$<1.0$ mmol/L ( $<40$ mg/dL)
Women	$<1.3$ mmol/L ( $<50$ mg/dL)	$<1.3$ mmol/L ( $<50$ mg/dL)
<b>Blood Pressure</b>		
	$\geq 130/85$ mmHg	$\geq 130/85$ mmHg
<b>Fasting Glucose Level</b>		
	$\geq 5.6$ mmol/L ( $>100$ mg/dL)	$\geq 5.6$ mmol/L ( $>100$ mg/dL)

WC = Waist circumference

## Metabolic Syndrome

- several definitions, most widely used are National Cholesterol Education Program (NCEP/ATP III, updated by American Heart Association) and International Diabetes Federation (IDF) definitions (see sidebar)
- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, hypertension, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include diabetes, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

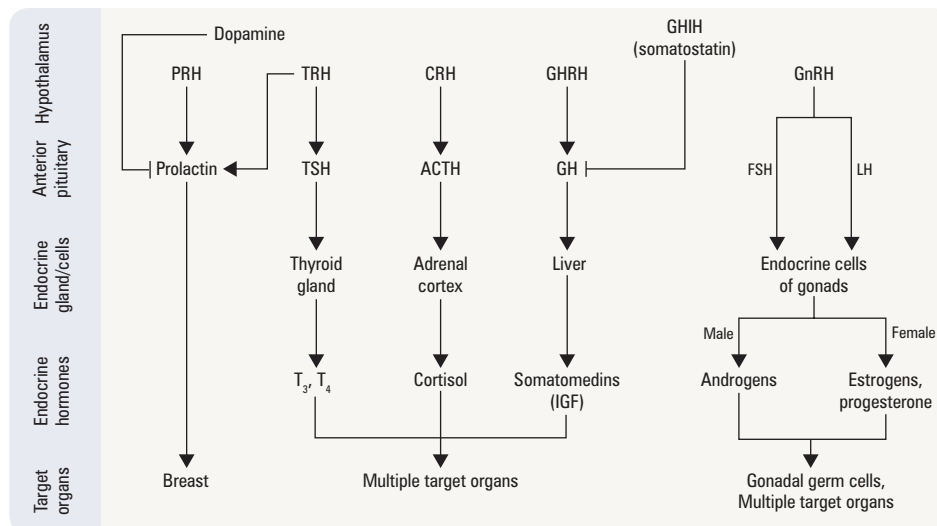
## Obesity

- see [Family Medicine](#), FM7



# Pituitary Gland

## Pituitary Hormones



**Figure 6. Hypothalamic-pituitary hormonal axes**

CRH = corticotropin-releasing hormone; GnRH = gonadotropin-releasing hormone; GHIH = growth hormone-inhibiting hormone; GHRH = growth hormone-releasing hormone; PRH = prolactin-releasing hormone; TRH = thyrotropin-releasing hormone

### Hypothalamic Control of Pituitary

- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control by dopamine, as well as GH and TSH which are inhibited by SS (somatostatin)
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

### Anterior Pituitary Hormones

- growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and prolactin (PRL)

### Posterior Pituitary (Hypothalamic) Hormones

- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus these hormones are stored and released from the posterior pituitary

**Table 15. The Physiology and Action of Pituitary Hormones**

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
<b>ACTH</b>	<ul style="list-style-type: none"> <li>• Stimulates growth of adrenal cortex and secretion of its hormones</li> </ul>	<ul style="list-style-type: none"> <li>• Polypeptide</li> <li>• Pulsatile and diurnal variation (highest in AM, lowest at midnight)</li> </ul>	<ul style="list-style-type: none"> <li>• Dexamethasone</li> <li>• Cortisol</li> </ul>	<ul style="list-style-type: none"> <li>• CRH</li> <li>• Metyrapone</li> <li>• Insulin-induced hypoglycemia</li> <li>• Vasopressin</li> <li>• Fever, pain, stress</li> </ul>
<b>GH</b>	<ul style="list-style-type: none"> <li>• Needed for linear growth</li> <li>• IGF-1 stimulates growth of bone and cartilage</li> </ul>	<ul style="list-style-type: none"> <li>• Polypeptide</li> <li>• Acts indirectly through serum factors synthesized in the liver: IGF-1 (somatomedin-C)</li> <li>• Serum GH undetectable for most of the day and suppressed after meals high in glucose</li> <li>• Sustained rise during sleep</li> </ul>	<ul style="list-style-type: none"> <li>• Glucose challenge</li> <li>• Glucocorticoids</li> <li>• Hypothyroidism</li> <li>• Somatostatin</li> <li>• Dopamine D2 receptor agonists</li> <li>• IGF-1 (long-loop)</li> <li>• Tonically by dopamine</li> </ul>	<ul style="list-style-type: none"> <li>• GHRH</li> <li>• Insulin-induced hypoglycemia</li> <li>• Exercise</li> <li>• REM sleep</li> <li>• Arginine, clonidine, propranolol, L-dopa</li> </ul>

**Table 15. The Physiology and Action of Pituitary Hormones** (continued)

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
<b>LH/FSH</b>	<ul style="list-style-type: none"> <li>Stimulate gonads via cAMP</li> <li>Ovary: <ul style="list-style-type: none"> <li>LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles</li> <li>FSH: growth of granulosa cells in ovarian follicle; controls estrogen formation</li> </ul> </li> <li>Testes: <ul style="list-style-type: none"> <li>LH: production of testosterone (Leydig cells)</li> <li>FSH: production of spermatozoa (Sertoli cells)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Polypeptide</li> <li>Glycoproteins (similar <math>\alpha</math> subunit as TSH and hCG)</li> <li>Secreted in pulsatile fashion</li> </ul>	<ul style="list-style-type: none"> <li>Estrogen</li> <li>Progesterone</li> <li>Testosterone</li> <li>Inhibin</li> <li>Continuous (i.e. non-pulsatile) GnRH infusion</li> </ul>	<ul style="list-style-type: none"> <li>Pulsatile GnRH</li> </ul>
<b>Prolactin</b>	<ul style="list-style-type: none"> <li>Promotes milk production</li> <li>Inhibits GnRH secretion</li> </ul>	<ul style="list-style-type: none"> <li>Polypeptide</li> <li>Episodic secretion</li> </ul>	<ul style="list-style-type: none"> <li>Dopamine</li> </ul>	<ul style="list-style-type: none"> <li>Sleep</li> <li>Stress, hypoglycemia</li> <li>Pregnancy, breastfeeding</li> <li>Mid-menstrual cycle</li> <li>Sexual activity</li> <li>TRH</li> <li>Drugs: psychotropics, antihypertensives, dopamine antagonists, opiates, high dose estrogen</li> </ul>
<b>TSH</b>	<ul style="list-style-type: none"> <li>Stimulates growth of thyroid and secretion of <math>T_3</math> and <math>T_4</math> via cAMP</li> </ul>	<ul style="list-style-type: none"> <li>Glycoprotein</li> </ul>	<ul style="list-style-type: none"> <li>Circulating thyroid hormones (<math>T_3</math>, <math>T_4</math>)</li> <li>Opiates, dopamine</li> </ul>	<ul style="list-style-type: none"> <li>TRH</li> <li>Epinephrine</li> <li>Prostaglandins</li> </ul>
<b>ADH</b>	<ul style="list-style-type: none"> <li>Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine</li> </ul>	<ul style="list-style-type: none"> <li>Octapeptide</li> <li>Secreted by posterior pituitary</li> <li>Osmoreceptors in hypothalamus detect serum osmolality</li> <li>Contracted plasma volume detected by baroreceptors is a more potent stimulus than <math>\uparrow</math> osmolality</li> </ul>	<ul style="list-style-type: none"> <li><math>\downarrow</math> serum osmolality</li> </ul>	<ul style="list-style-type: none"> <li>Hypovolemia or <math>\downarrow</math> effective circulatory volume</li> <li><math>\uparrow</math> serum osmolality</li> <li>Stress, pain, fever, paraneoplastic</li> <li>Lung or brain pathology</li> </ul>
<b>Oxytocin</b>	<ul style="list-style-type: none"> <li>Causes uterine contraction</li> <li>Breast milk secretion</li> </ul>	<ul style="list-style-type: none"> <li>Not a peptide</li> <li>Secreted by posterior pituitary</li> </ul>	<ul style="list-style-type: none"> <li>EtOH</li> </ul>	<ul style="list-style-type: none"> <li>Suckling</li> <li>Distention of female genital tract during labour via stretch receptors</li> </ul>

## Growth Hormone (GH)



### GH DEFICIENCY

- cause of short stature in children (see [Pediatrics](#), P27)
- controversial significance in adults; often not clinically apparent, may present as fatigue



### GH EXCESS

- in children (before epiphyseal fusion) leads to gigantism
- in adults (after epiphyseal fusion) leads to acromegaly



#### Signs and Symptoms of Acromegaly:

##### ABCDEF

- Arthralgia/Arthritis
- Blood pressure raised
- Carpal tunnel syndrome
- Diabetes
- Enlarged organs
- Field defect (visual)

### Etiology

- GH secreting pituitary adenoma, carcinoid or pancreatic islet tumours secreting ectopic GHRH resulting in excess GH

### Pathophysiology

- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in growth hormone excess states secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

### Clinical Features

- enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, thickening of skin, increased sebum production, sweating, acne, sebaceous cysts, fibromata mollusca, acanthosis nigricans, arthralgia, carpal tunnel syndrome, degenerative osteoarthritis, thyromegaly, renal calculi, hypertension, cardiomyopathy, obstructive sleep apnea, colonic polyps and DM

**Investigations**

- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- elevated serum insulin-like growth factor-1 (IGF-1) is usually first line diagnostic test

**Treatment**

- surgery, octreotide (somatostatin analogue), dopamine agonist (bromocriptine/cabergoline), growth hormone receptor antagonist (pegvisomant), radiation

## Prolactin (PRL)

**HYPERPROLACTINEMIA****Etiology**

- pregnancy and breastfeeding
- prolactinoma: most common pituitary adenoma (prolactin-secreting tumours may be induced by estrogens and grow during pregnancy)
- pituitary masses with pituitary stalk compression causing reduced dopamine inhibition of prolactin release
- primary hypothyroidism (increased TRH)
- decreased clearance due to chronic renal failure or severe liver disease (prolactin is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics (common), antidepressants, antihypertensives, anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide/domperidone), H<sub>2</sub>-blockers (ranitidine)
- macroprolactinemia (high molecular weight prolactin also known as big big prolactin)

**Clinical Features**

- galactorrhea (secretion of breast milk in women and, rarely, men), infertility, hypogonadism, amenorrhea, erectile dysfunction

**Investigations**

- serum PRL, TSH, liver enzyme tests, creatinine
- MRI

**Treatment**

- long-acting dopamine agonist: bromocriptine, cabergoline or quinagolide (Norprolac®)
- surgery ± radiation (rare)
- prolactin-secreting tumours are very slow-growing and sometimes require no treatment
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

**Approach to Nipple Discharge**

- Differentiate between galactorrhea (fat droplets present) versus breast discharge (usually unilateral, may be bloody or serous)
- If galactorrhea, determine if physiologic (e.g. pregnancy, lactation, stress) versus pathologic
- If abnormal breast discharge, must rule out a breast malignancy

## Thyroid Stimulating Hormone (TSH)

- see *Thyroid*, E20



## Adrenocorticotrophic Hormone (ACTH)

- see *Adrenal Cortex*, E29



## Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)

- see *Gynecology*, GY4

**HYPOGONADOTROPIC HYPOGONADISM****Clinical Features**

- hypogonadism, amenorrhea, erectile dysfunction (see *Urology*, U30), loss of body hair, fine skin, testicular atrophy, failure of pubertal development

**Treatment**

- Pergonal® (combined FSH/LH hormone therapy), hCG, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone



**HYPERGONADOTROPIC HYPOGONADISM**

- 2° hypersecretion in gonadal failure (e.g. in menopause)

**Antidiuretic Hormone (ADH)****DIABETES INSIPIDUS (DI)****Definition**

- disorder resulting from deficient ADH action causing passage of large volumes of dilute urine

**Etiology and Pathophysiology**

- central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, stalk lesion, hydrocephalus, histiocytosis X, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI
- psychogenic polydipsia and osmotic diuresis must be ruled out

**Clinical Features**

- passage of large volumes of dilute urine, polydipsia, dehydration; hypernatremia can develop with lack of access to water or impaired thirst mechanism

**Diagnostic Criteria**

- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
- response to exogenous ADH (DDAVP) will distinguish central from nephrogenic DI

**Treatment**

- DDAVP/vasopressin for central DI
- chlorpropamide, clofibrate, thiazides, NSAIDs or carbamazepine as second line or for partial DI
- nephrogenic DI treated with solute restriction NSAIDs and thiazide diuretics; DDAVP (if partial)

**Diagnosing Subtypes of DI with DDAVP Response**

Concentrated urine = Central  
No effect = Nephrogenic

**SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)****Diagnostic Criteria**

- hyponatremia with corresponding plasma hypo-osmolality, urine sodium concentration above 40 mEq/L, urine less than maximally diluted (>100 mOsm/kg), euvolemia (edema absent), and absence of adrenal, renal or thyroid insufficiency

**Etiology and Pathophysiology**

- stress (pain, nausea, post-surgical)
- malignancy (lung, pancreas, lymphoma)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
- respiratory disease (TB, pneumonia, empyema)
- drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

**Treatment**

- treat underlying cause, fluid restriction (800-1000 mL/day), vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), and demeclocycline (antibiotic with anti-ADH properties, rarely-used) fludrocortisone, furosemide

**SIADH vs. Cerebral Salt Wasting (CSW)**

CSW can occur in cases of subarachnoid hemorrhage. Na<sup>+</sup> is excreted by malfunctioning renal tubules, mimicking findings of SIADH. Hallmark is hypovolemia

**Presentations of Pituitary Lesions:**

- Mass effect (visual field deficits, diplopia, ptosis, headaches, CSF leak)
- Hyperfunction
- Hypofunction

**Important Deficiencies to Recognize are:**

- Adrenal insufficiency
- Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis.

**Pituitary Pathology****PITUITARY ADENOMA** (see [Neurosurgery](#), NS14)**Clinical Features**

- local mass effects
  - visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies), headaches; increased ICP is rare
- hypofunction
  - hypopituitarism (see sidebar)
- hyperfunction
  - PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing's disease = Cushing's syndrome caused by a pituitary tumour)
  - tumours secreting LH, FSH and TSH are rare

### Investigations

- radiological evaluation (MRI is imaging procedure of choice)
- formal visual field testing
- hypothalamic-pituitary hormonal function

### HYPOPITUITARISM

#### Etiology (the eight Is)

- Invasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke's cleft, arachnoid or dermoid), metastases
- Infarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive post-partum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache and altered level of consciousness; can be fatal if not recognized and treated early)
- Infiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- Infectious
  - syphilis, TB, fungal (histoplasmosis), parasitic (toxoplasmosis)
- Injury
  - severe head trauma
- Immunologic
  - autoimmune destruction
- Iatrogenic
  - following surgery or radiation
- Idiopathic
  - familial forms, congenital midline defects

#### Investigations

- triple bolus test
  - stimulates release of all anterior pituitary hormones in normal individuals
  - rapid sequence of IV infusion of insulin, GnRH and TRH
  - insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and ACTH
  - GnRH (100 µg IV push) → increased LH and FSH
  - TRH (200 µg IV push over 60 s) → increased TSH and PRL (no longer available)



#### The Pituitary Hormones

Order they are usually lost with compression by a mass:

"Go Look For The Adenoma Please"

GH, LH, FSH, TSH, ACTH, PRL +

posterior pituitary hormones: ADH and oxytocin



## Thyroid

### Thyroid Hormones

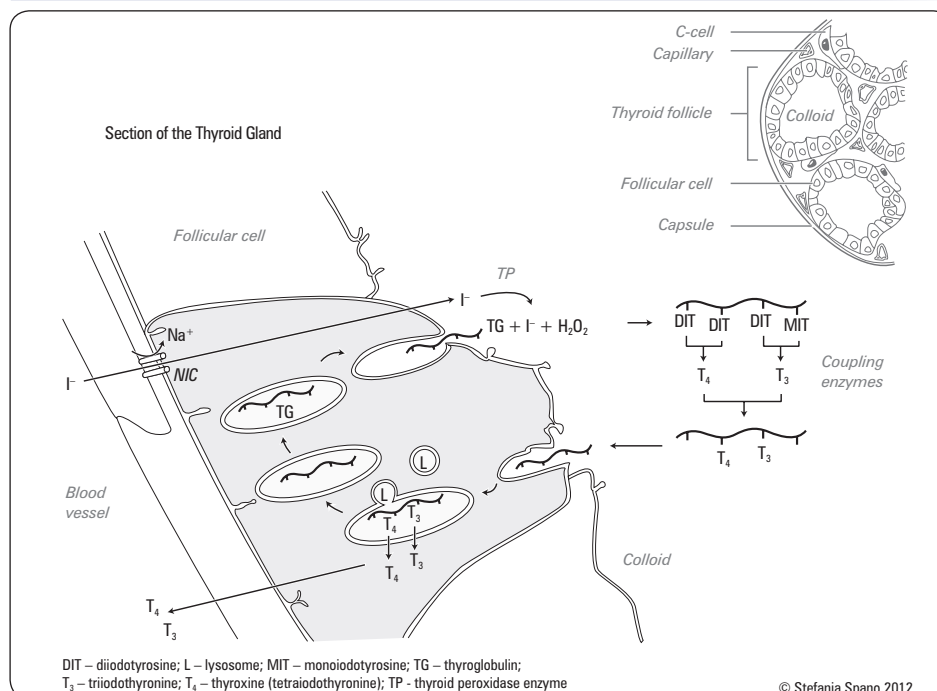


Figure 7. Thyroid hormone synthesis

### Synthetic Function of Thyroid Gland

- the synthesis of thyroid hormones  $T_4$  (thyroxine) and  $T_3$  (triiodothyronine) by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, and release of  $T_3$  and  $T_4$
- free  $T_4$  (0.03%) and free  $T_3$  (0.3%) represent the hormonally active fraction of thyroid hormones
  - the remaining fraction is bound to thyroxine binding globulin (TBG) and albumin and is biologically inactive
- $T_3$  is more biologically active (3-8x more potent), but  $T_4$  has a longer half-life
- 85% of  $T_4$  is converted to  $T_3$  or reverse  $T_3$  (RT3) in the periphery by deiodinases
- RT3 is metabolically inactive but produced in times of stress to decrease metabolic activity
- most of the plasma  $T_3$  pool is derived from the peripheral conversion of  $T_4$
- calcitonin, a peptide hormone, is also produced in the thyroid, by the parafollicular cells or C cells
  - it functions by inhibiting osteoclast activity and increasing renal calcium excretion

### Role of Thyroid Hormones

- thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
- action of these hormones is diffuse, effecting nearly every organ system
- they produce an increase in basal metabolic rate, including: increased  $Na^+/K^+$ ATPase activity, increase  $O_2$  consumption, increased respiration, heat generation, and increased cardiovascular activity
- also play crucial role during fetal life in both neurological and somatic development

### Regulation of Thyroid Function

- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
  - $T_3$  negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
- intrathyroid (autoregulation)
  - increasing iodide supply inhibits iodide organification, thus decreasing  $T_3$  and  $T_4$  synthesis (Wolff-Chaikoff effect)
  - there is varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of  $T_3$  to  $T_4$  in iodide deficiency
  - increased activity of peripheral 5' deiodinase in hypothyroidism increases  $T_3$  production despite low  $T_4$  levels



#### Thyroid Assessment

- Serum thyroid hormones (TSH,  $T_3$ ,  $T_4$ )
- Antibodies
- Thyroglobulin
- Thyroid ultrasound
- Nuclear uptake and scan
- Biopsy (FNA)



#### Patterns of Hormone Levels

	TSH	$T_3$ , $T_4$
1° Hyper	↓	↑
2° Hyper	↑	↑
1° Hypo	↑	↓
2° Hypo	↓	↓



#### Does this Patient have a Goitre?

##### From The Rational Clinical Examination

JAMA 2009; <http://www.jamaevidence.com/content/3480618>

**Study:** Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of a goitre.

**Results:** Clinical diagnosis was based on degree of lateral prominence, visibility, and palpability of the thyroid gland. No evidence exists to support the superiority of any one method.

The combined results of 4 studies detail the predictive utility of assessing grades of thyroid gland weight:

Weight	Reference	LR+	95% CI
0-20 g	normal	0.15	(0.10-0.21)
20-40 g	1-2x	1.9	(1.1-3.0)
>40 g	>2x	25.0	(2.6-175)

Alternatively, defining a goiter as mass larger than the distal phalanx of the thumb has been shown to have an LR+ of 3.0 (95% CI, 2.5-3.5) and LR- of 0.30 (95% CI, 0.24-0.37) in children, and an LR+ of 4.7 (95% CI, 3.6-6.0) and LR- of 0.08 (95% CI, 0.02-0.27) for the presence of a goitre.

**Conclusions:** Use of weight of thyroid tissue is an appropriate method of diagnosing a goitre, while comparing the size of thyroid mass to the distal phalanx of the thumb may be a useful alternative.

## Tests of Thyroid Function and Structure

### TSH

- sensitive TSH (sTSH) is the best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low because of negative feedback from increased levels of circulating  $T_3$  and  $T_4$
  - secondary: increased TSH results in increased  $T_3$  and  $T_4$
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from  $T_3$  and  $T_4$
  - secondary: TSH is low or normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

### Free $T_3$ and Free $T_4$

- indications: if secondary or tertiary (hypothalamic) hyper/hypothyroidism is suspected, or if normal TSH levels despite symptoms of hyper/hypothyroidism
- standard assessment of thyroid function measures TSH and if necessary free  $T_4$ . Free  $T_3$  should be measured if TSH is suppressed and free  $T_4$  is normal to rule out  $T_3$  toxicosis

### Thyroid Autoantibodies

- thyroglobulin antibodies (TgAb), thyroid peroxidase antibodies, TSH receptor inhibiting antibodies
  - increased in Hashimoto's disease; normal variant in 10-20% of individuals
- thyroid stimulating immunoglobulin (TSI)
  - increased in Graves' disease

### Plasma Thyroglobulin

- used to monitor residual thyroid activity post-thyroidectomy, e.g. for thyroid cancer recurrence
- normal or elevated levels may suggest persistent, recurrent or metastatic disease, especially on stimulation

### Serum Calcitonin

- not routinely done to investigate thyroid nodules
- ordered if suspicion of medullary thyroid carcinoma or family history of MEN IIa or IIb syndromes

### Thyroid Imaging/Scans

- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
  - to measure size of gland, solid vs. cystic nodule, facilitate fine needle aspirate biopsy (FNAB)
- radioisotope thyroid scan (Technetium-99)
  - *test of structure*: order if there is a thyroid nodule and patient is hyperthyroid with low TSH
  - differentiates between hot (functioning → excess thyroid hormone production) and cold (non-functioning) nodules
    - ♦ hot nodule → very low chance malignancy; treat hyperthyroidism
    - ♦ cold nodule → ~5% chance malignancy; further work-up required (U/S and FNAB)
- radioactive iodine uptake (RAIU)
  - *test of function*: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland *in vivo*
  - if ↑ uptake (i.e. incorporated) → gland is overactive (hyperthyroid)
  - if ↓ uptake (i.e. not incorporated) → gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)

### Thyroid Biopsy

- fine needle aspiration (FNA) for cytology
  - differentiates between benign and malignant disease
  - best done under ultrasound guidance
  - accuracy decreased if nodule is greater than 50% cystic, or if nodule located posteriorly in the gland

**Table 16. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism**

	Hyperthyroidism	Hypothyroidism
<b>TSH</b>	<ul style="list-style-type: none"> <li>• Decreased in 1° hyperthyroidism</li> <li>• Increased in 2° hyperthyroidism</li> </ul>	<ul style="list-style-type: none"> <li>• Increased in 1° hypothyroidism</li> <li>• Decreased in 2° hypothyroidism</li> </ul>
<b>Free T<sub>4</sub></b>	<ul style="list-style-type: none"> <li>• Increased in 1° hyperthyroidism</li> <li>• Increased in 2° hyperthyroidism</li> </ul>	<ul style="list-style-type: none"> <li>• Decreased in 1° hypothyroidism</li> <li>• Decreased in 2° hypothyroidism</li> </ul>
<b>Antibodies</b>	Graves': thyroid stimulating Ig (TSI)	Hashimoto's: antithyroid peroxidase (TPO)
<b>RAIU</b>	Increased uptake: <ul style="list-style-type: none"> <li>• Graves'</li> <li>• Toxic Multinodular goitre</li> <li>• Toxic adenoma</li> </ul>	Decreased uptake <ul style="list-style-type: none"> <li>• Subacute thyroiditis</li> <li>• Recent iodine load</li> <li>• Exogenous thyroid hormone</li> </ul>
<b>Radioisotope Thyroid Scan</b>	<ul style="list-style-type: none"> <li>• Graves': homogenous diffuse uptake</li> <li>• Multinodular goitre: heterogenous uptake</li> <li>• Toxic adenoma: single intense area of uptake with suppression elsewhere</li> </ul>	



#### Caution with Amiodarone

**Amiodarone-Induced Hypothyroidism (AIH):** AIH occurs more often in iodine-sufficient areas, and is more common in populations with a higher prevalence of autoimmune thyroid disease, such as women and the elderly. AIH can also occur in patients without pre-existing thyroid dysfunction.

**Amiodarone-Induced Thyrotoxicosis (AIT):** AIT occurs more often in iodine-deficient areas. It may occur in patients with pre-existing thyroid deficiencies, as an iodine load on an already dysfunctional thyroid may result in excessive thyroid hormone synthesis and release. AIT may also occur in patients without thyroid abnormalities through a cytotoxic mechanism that results in leakage of thyroid hormone into the systemic circulation.



#### Common Etiologies

Thyrotoxicosis	Hypothyroidism
Graves' Disease	Hashimoto's
Toxic Nodular Goitre	Congenital
Toxic Nodule	Iatrogenic (thionamides, radioactive iodine or surgery)
Thyroiditis	Hypothyroid phase of thyroiditis

## Thyrotoxicosis

### Definition

- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

### Epidemiology

- 1% of general population have hyperthyroidism
- F:M = 5:1

### Etiology and Pathophysiology

**Table 17. Differential Diagnosis of Thyrotoxicosis**

Disorder	TSH	Free T <sub>4</sub> /T <sub>3</sub>	Thyroid Antibodies	RAIU	Other
<b>HYPERTHYROIDISM</b>					
Graves' Disease	Decreased	Increased	TSI	Increased	
Toxic Nodular Goitre	Decreased	Increased	None	Increased	Heterogeneous uptake on scan
Toxic Nodule	Decreased	Increased	None	Increased	Hot nodule on scan
<b>THYROIDITIS</b>					
Subacute, Silent, Postpartum	Decreased	Increased	Up to 50% of cases	Decreased (becomes increased once entering hypothyroid phase, when TSH rises)	In classical subacute painful thyroiditis, ESR increased
<b>EXTRATHYROIDAL SOURCES OF THYROID HORMONE</b>					
Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma)	Decreased	Increased	None	Decreased	
Exogenous (drugs)	Decreased	Increased (T <sub>4</sub> would be decreased if taking T <sub>3</sub> )	None	Decreased	

**Table 17. Differential Diagnosis of Thyrotoxicosis (continued)**

Disorder	TSH	Free T <sub>4</sub> /T <sub>3</sub>	Thyroid Antibodies	RAIU	Other
<b>EXCESSIVE THYROID STIMULATION</b>					
Pituitary thyrotrophoma	Increased	Increased	None	Increased	
Pituitary thyroid hormone receptor resistance	Increased	Increased	None	Increased	
Increased hCG (e.g. pregnancy)	Decreased	Increased	None	Increased DO NOT DO THIS TEST IN PREGNANCY	

**Clinical Features****Table 18. Clinical Features of Thyrotoxicosis**

<b>General</b>	Fatigue, heat intolerance, irritability, fine tremor
<b>CVS</b>	Tachycardia, atrial fibrillation, palpitations Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation
<b>GI</b>	Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)
<b>Neurology</b>	Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians)
<b>GU</b>	Oligomenorrhea, amenorrhea, decreased fertility
<b>Dermatology</b>	Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema Graves' disease: clubbing (acropachy), pretibial myxedema (rare)
<b>MSK</b>	Decreased bone mass, proximal muscle weakness
<b>Hematology</b>	Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)
<b>Eye</b>	Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjunctival injection

**Treatment**

- thionamides: PTU or MMI; MMI recommended (except in first trimester pregnancy)
- $\beta$ -blockers for symptom control
- radioactive iodine thyroid ablation for Graves' disease
- surgery in the form of hemi, sub-total, or complete thyroidectomy

**Graves' Disease****Definition**

- syndrome characterized by hyperthyroidism with any of: diffuse goitre, ophthalmopathy, dermopathy

**Epidemiology**

- most common cause of thyrotoxicosis
- occurs at any age with peak in 3rd and 4th decade
- F > M = 7:1, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA B8 and DR3
- may be associated with other inherited autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

**Etiology and Pathophysiology**

- autoimmune disorder due to a defect in T-suppressor cells
- B lymphocytes produce TSI that binds the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, lithium therapy, viral or bacterial infections, glucocorticoid withdrawal
- ophthalmopathy a result of increased tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit. This leads to fluid accumulation and displacement of the eye ball forward
- dermopathy may be related to cutaneous glycosaminoglycan deposition

**Clinical Features**

- signs and symptoms of thyrotoxicosis
- diffuse thyroid goitre  $\pm$  thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity if Graves' (plus signs of hyperthyroidism: lid retraction, characteristic stare)

**Signs and Symptoms of HYPERthyroidism**

Tremor  
Heart rate up  
Yawning (fatigued)  
Restlessness  
Oligomenorrhea/amenorrhea  
Intolerance to heat  
Diarrhea  
Irritability  
Sweating  
Muscle wasting/weight loss

**Caution with Thionamides**

These drugs are effective in controlling hyperthyroidism and induce permanent remission in 20-30% of patients with Graves' disease. They inhibit thyroid hormone synthesis. They are most often employed to achieve a euthyroid state before definitive treatment. Adverse effects include teratogenicity, agranulocytosis, hepatotoxicity and ANCA-positive vasculitis.

**Graves' Ophthalmopathy****NO SPECS (in order of changes usually)**

No signs  
Only signs: lid lag, lid retraction  
Soft tissue: periorbital puffiness, conjunctival injection, chemosis  
Proptosis/Exophthalmos  
Extraocular (diplopia)  
Corneal abrasions (since unable to close eyes)  
Sight loss

- dermatopathy (rare): pretibial myxedema (thickening of dermis that manifests as *non-pitting* edema)
- acropachy: clubbing and thickening of distal phalanges

### Investigations

- low TSH
- increased free  $T_4$  (and/or increased  $T_3$ )
- positive for TSI
- increased radioactive iodine uptake
- diffuse high uptake on thyroid scan (only do this test in the presence of nodule)

### Treatment

- thionamides
  - propylthiouracil (PTU) or methimazole (MMI)
  - inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines. PTU also inhibits peripheral deiodination of  $T_4$  to  $T_3$
  - continue treatment until remission occurs (20-40% of patients achieve spontaneous remission at 6-18 mo of treatment)
  - small goitre and recent onset are good indicators for long-term remission with medical therapy
  - major side effects: hepatitis, agranulocytosis and fever/arthritis
  - minor side effects: rash
  - iodinated contrast agents: sodium ipodate and iopanoic acid can inhibit conversion of  $T_4$  to  $T_3$  and are especially effective in combination with MMI
  - MMI preferred vs. PTU due to longer duration of action (once daily for most), more rapid efficacy, and lower incidence of side effects
  - MMI contraindicated in pregnancy (teratogenic), use PTU
- symptomatic treatment with  $\beta$ -blockers
- thyroid ablation with radioactive  $^{131}\text{I}$  if PTU or MMI trial does not produce disease remission
  - high incidence of hypothyroidism after  $^{131}\text{I}$  requiring lifelong thyroid hormone replacement
  - contraindicated in pregnancy
- subtotal or total thyroidectomy (indicated rarely for large goiters, suspicious nodule for CA, if patient is intolerant to thionamides and refusing RAI ablation)
  - risks include hypoparathyroidism and vocal cord palsy
- ophthalmopathy/orbitopathy
  - smoking cessation is most important
  - prevent drying
  - high dose prednisone in severe cases
  - orbital radiation, surgical decompression

### Prognosis

- course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
- lifetime follow-up needed
- risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively



#### Radioiodine Therapy for Graves' Disease and the Effect on Ophthalmopathy – A Systematic Review

*Clin Endocrinol* 2008;69:943-950

**Purpose:** To assess whether radioiodine therapy (RAI) for Graves' disease (GD) is associated with increased risk of ophthalmopathy compared with antithyroid drugs (ATDs) or surgery. To assess the efficacy of glucocorticoid prophylaxis in the prevention of occurrence or progression of Graves' ophthalmopathy (GO), when used with RAI.

**Study Selection:** Randomized controlled trials regardless of language or publication status.

**Results:** RAI was associated with an increased risk of GO compared with ATD (Relative Risk (RR) 4.23, 95% confidence interval (CI): 2.04 to 8.77) but compared with thyroidectomy, there was no statistically significant increased risk (RR 1.59, 95% CI 0.89 to 2.81). The risk of severe GO was also increased with RAI compared with ATD (RR 4.35, 95% CI 1.28 to 14.73). Prednisolone prophylaxis for RAI was highly effective in preventing the progression of GO in patients with pre-existing GO (RR 0.03; 95% CI 0.00 to 0.24). The use of adjunctive ATD with RAI was not associated with any significant benefit on the course of GO.

**Conclusions:** RAI therapy for GD is associated with a small but definite increased risk of development or worsening of GO compared with ATDs. Steroid prophylaxis is beneficial for patients with pre-existing GO.



#### Other Medications Used in the Treatment of Graves'

**Glucocorticoids** have been useful in the treatment of severe Graves' hyperthyroidism and thyroid storm, by inhibiting the conversion of peripheral  $T_4$  to  $T_3$ .

**Lithium** is also used to treat Graves' hyperthyroidism. It acts by blocking thyroid hormone release, but its toxicity has limited its use in practice.

## Subacute Thyroiditis (Thyrototoxic Phase)

### Definition

- acute inflammatory disorder of the thyroid gland characterized by an initial thyrotoxic state followed by hypothyroidism eventually followed by euthyroidism in most cases
- two subtypes: painful and painless

### Etiology and Pathophysiology

- acute inflammation of the thyroid gland characterized by giant cells and lymphocytes
- disruption of thyroid follicles by inflammatory process results in the release of stored hormone rather than excessive production of new thyroid hormone
- painful = viral (usually preceded by URTI), De Quervain's (granulomatous thyroiditis)
- painless = postpartum, auto-immune, lymphocytic
  - occurs in 5-10% of postpartum mothers and is symptomatic in 1/3 of patients

### Clinical Features

- thyroid gland enlargement
- two forms
  - painful ("De Quervain's") thyroid, ears, jaw and occiput
  - painless ("Silent")



- fever and malaise may be present, especially in De Quervain's
- postpartum: thyrotoxicosis 2-3 mo postpartum with a subsequent hypothyroid phase at 4-8 mo postpartum
- may be mistakenly diagnosed as postpartum depression

**Laboratory Investigations**

- initial elevated free  $T_4$ ,  $T_3$ , low TSH, RAIU markedly reduced
- marked elevation of ESR in painful variety only
- as disease progresses values consistent with hypothyroidism may appear
- rise in RAIU reflects gland recovery

**Treatment**

- painful – high dose NSAIDs, prednisone may be required for severe pain, fever, or malaise
- iodinated contrast agents (e.g. iopanoic acid, ipodate) to inhibit peripheral conversion of  $T_4$  to  $T_3$
- $\beta$ -adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms in both subtypes
- if symptomatically hypothyroid, may treat short-term with thyroxine

**Prognosis**

- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis
- postpartum: most resolve spontaneously without need for supplementation, however may recur with subsequent pregnancies

## Toxic Adenoma/Toxic Multinodular Goitre

**Etiology and Pathophysiology**

- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting  $T_3$  and  $T_4$
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre [Plummer's disease])

**Clinical Features**

- goitre with adenomatous changes
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- atrial fibrillation is a common presentation in the elderly
- seen most frequently in elderly people, often with presentation of atrial fibrillation

**Investigations**

- low TSH, high  $T_3$  and  $T_4$
- thyroid scan with increased uptake in nodule(s) and suppression of the remainder of the gland

**Treatment**

- initiate therapy with PTU or MMI to attain euthyroid state in order to avoid radiation thyroiditis
- use high dose radioactive iodine to ablate tissue over weeks
- $\beta$ -blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as 1st line treatment

## Thyrotoxic Crisis/Thyroid Storm

**Definition**

- acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism – medical emergency!
- rare, but serious with mortality rate between 20-30%

**Etiology and Pathophysiology**

- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

**Differential Diagnosis**

- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

**Clinical Features**

- hyperthyroidism
- extreme hyperthermia, tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
- tachyarrhythmia, congestive heart failure, shock
- mental status changes ranging from delirium to coma

### Laboratory Investigations

- increased free  $T_3$  and  $T_4$ , undetectable TSH
- $\pm$  anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

### Treatment

- principles are the same as in hyperthyroidism except use higher doses and frequencies
- initiate prompt therapy; do not wait for confirmation from lab
- supportive: fluid and electrolytes, diuresis, vasopressors, cooling blanket, and acetaminophen for hyperthermia
- propranolol (IV) for tachycardia and to decrease peripheral conversion of  $T_4$  to  $T_3$  (watch for CHF)
- high dose PTU/MMI
- iodide (NaI, KI, Lugol's solution) to inhibit release of thyroid hormone, given after PTU
- iodinated radiocontrast solutions such as iopanoic acid inhibit both peripheral conversion of  $T_4$  to  $T_3$  and release of thyroid hormone
- lithium to inhibit release of thyroid hormone
- dexamethasone to block peripheral conversion, to lower body temperature, and to treat possible underlying autoimmune condition
- if extreme plasmapheresis or dialysis to remove high circulating thyroid hormone
- treat precipitant

### Prognosis

- probably <20% mortality rate if rapidly recognized and treated

## Hypothyroidism

### Definition

- clinical syndrome caused by cellular responses to insufficient thyroid hormone production

### Epidemiology

- 2-3% of general population
- F:M = 10:1
- 10-20% of women over age 50 have subclinical hypothyroidism (normal  $T_4$ , TSH mildly elevated)
- iodine deficiency most common cause worldwide, but not in North America

### Etiology and Pathophysiology

- primary hypothyroidism (90%)
  - inadequate thyroid hormone production secondary to intrinsic thyroid defect
  - iatrogenic: post-ablative ( $^{131}\text{I}$  or surgical thyroidectomy)
  - autoimmune: Hashimoto's thyroiditis, chronic thyroiditis, idiopathic, burnt out Graves'
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4000 births)
  - neoplasia
- secondary hypothyroidism: pituitary hypothyroidism
  - insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
  - decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

**Table 19. Interpretation of Serum TSH and Free  $T_4$  in Hypothyroidism**

	Serum TSH	Free $T_4$
Overt Primary Hypothyroidism	Increased	Decreased
Subclinical Primary Hypothyroidism	Increased	Normal
Secondary Hypothyroidism	Decreased or not appropriately elevated	Decreased



#### Thyroid Hormone Replacement for Subclinical Hypothyroidism

*Cochrane DB Syst Rev 2007;3:CD003419*

**Purpose:** To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.

**Study Selection:** RCTs comparing thyroid hormone replacement with placebo in adults with subclinical hypothyroidism. Minimum duration of follow-up was one month.

**Results:** No trial assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation. Only four studies reported adverse events with no statistically significant differences between groups.

**Conclusions:** In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.



#### Signs and Symptoms of Hypothyroidism

##### HIS FIRM CAP

Hypoventilation  
Intolerance to cold  
Slow HR  
Fatigue  
Impotence  
Renal impairment  
Menorrhagia/amenorrhea  
Constipation  
Anemia  
Paresthesia

## Clinical Features

**Table 20. Clinical Features of Hypothyroidism**

<b>General</b>	Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia
<b>CVS</b>	Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart
<b>Respiratory</b>	Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia
<b>GI</b>	Weight gain despite poor appetite, constipation
<b>Neurology</b>	Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes"), carpal tunnel syndrome, asymptomatic increase in CK, seizures
<b>GU</b>	Menorrhagia, amenorrhea, impotence
<b>Dermatology</b>	Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discolouration (carotenemia)
<b>Hematology</b>	Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto's thyroiditis

### Treatment

- L-thyroxine (dose range: 0.05-0.2 mg PO OD ~1.6 µg/kg/d)
- usually require 1.6 times their weight in kg as the dose in µg/d
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up TSH with patient annually
- secondary/tertiary hypothyroidism:
  - need to rule out and/or treat adrenal insufficiency first
  - monitor via measurement of free T<sub>4</sub> (TSH is unreliable in this setting)

### CONGENITAL HYPOTHYROIDISM

- see [Pediatrics](#), P30



## Hashimoto's Thyroiditis

- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from the start
  - associated with thyroid lymphoma

### Etiology and Pathophysiology

- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na<sup>+</sup>/I symporter

### Risk Factors

- female gender
- genetic susceptibility: increased frequency in patients with Down's syndrome, Turner's syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake
- stress and infection

### Investigations

- high TSH, low T<sub>4</sub> (not necessary to measure T<sub>3</sub> as it will be low as well)
- presence of thyroid peroxidase and thyroglobulin antibodies in serum

### Treatment

- if hypothyroid, replace with L-thyroxine (analog of T<sub>4</sub>)

## Myxedema Coma

### Definition

- severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – medical emergency!
- rare, but serious mortality when it occurs (up to 60%, despite therapy)

### Clinical Features

- hallmark symptoms of decreased mental status and hypothermia; hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized edema often present

### Investigations

- decreased  $T_4$ , increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

### Treatment

- aggressive treatment required
- ABCs: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated; also consider  $T_3$  therapy
- supportive measures: mechanical ventilation, fluids, vasopressor drugs, passive rewarming, IV dextrose
- monitor for arrhythmia

## Sick Euthyroid Syndrome (SES)

### Definition

- changes in circulating thyroid hormones amongst patients with serious illness, trauma or stress
- not due to intrinsic thyroid or pituitary disease
- initially low free  $T_3$  may be followed by low TSH and if severe illness low free  $T_4$ . With recovery of illness TSH may overshoot and become transiently high

### Pathophysiology

- abnormalities in SES include alterations in
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
  - thyroid function itself

### Labs

- initially decreased free  $T_3$  followed by decreased TSH and finally decreased free  $T_4$

### Treatment

- treat the underlying disease; thyroid hormone replacement worsens outcomes
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

## Non-Toxic Goitre

### Definition

- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

### Pathophysiology

- the appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages: goitre is usually diffuse
  - later stages: multinodular non-toxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

### Etiology

- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

### Treatment

- remove goitrogens
- radioiodine therapy (need very high doses since non-toxic, used as last resort)
- suppression with L-thyroxine (rarely done)
- surgery may be necessary for severe compressive symptoms

### Complications

- compression of neck structures causing stridor, dysphagia, pain and hoarseness
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

## Thyroid Nodules

### Definition

- clearly defined discrete mass, separated from the thyroid parenchyma
- palpable nodules are found in approximately 5% of the population
- M:F = 1:4

### Etiology

- benign tumours (e.g. colloid nodule, follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

### Investigations

- thyroid ultrasound to determine size and characteristics (cystic vs. solid vs. mixed)
- thyroid function tests (TSH)
- thyroid scan only if TSH is low to determine if nodule is hot (i.e. significant  $^{131}\text{I}$  uptake into nodule) which signifies very low malignant potential
- FNA for all nodules >1-1.5 cm, if not a hot nodule

## Thyroid Malignancies

- see [Otolaryngology](#), OT37



## Adrenal Cortex

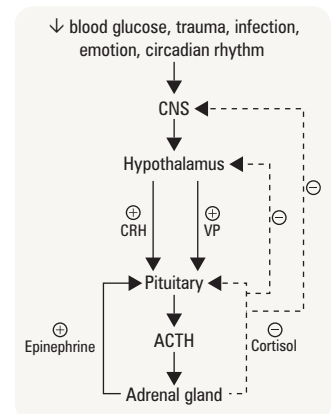
### Adrenocorticotropin Hormone (ACTH)

- a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400; trough: 1800-2400)
- secretion regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)
- stimulates growth of adrenal cortex and release of glucocorticoids, androgens and, to a limited extent, mineralocorticoids
- some melanocyte stimulating activity

### Adrenocortical Hormones

#### Aldosterone

- a mineralocorticoid which regulates extracellular fluid (ECF) volume through  $\text{Na}^+$  (and  $\text{Cl}^-$ ) retention and  $\text{K}^+$  (and  $\text{H}^+$ ) excretion (stimulates distal tubule  $\text{Na}^+/\text{K}^+$  ATPase)
- regulated by the renin-angiotensin-aldosterone system (Figure 10)
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone  $\rightarrow$  volume expansion) and short loop (angiotensin II  $\rightarrow$  peripheral vasoconstriction)



**Figure 8. Regulation of CRH-ACTH-adrenal gland axis**

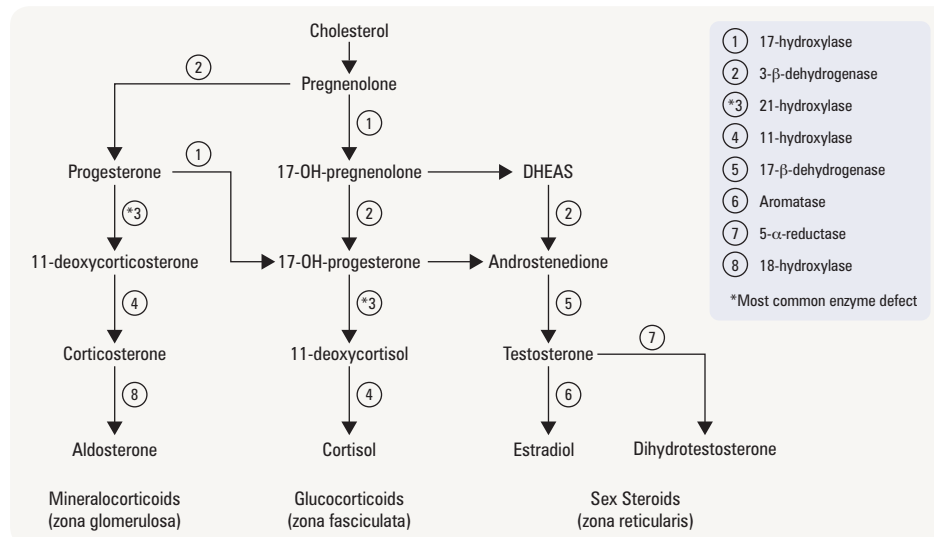


Figure 9. Pathways of major steroid synthesis in the adrenal gland and their enzymes

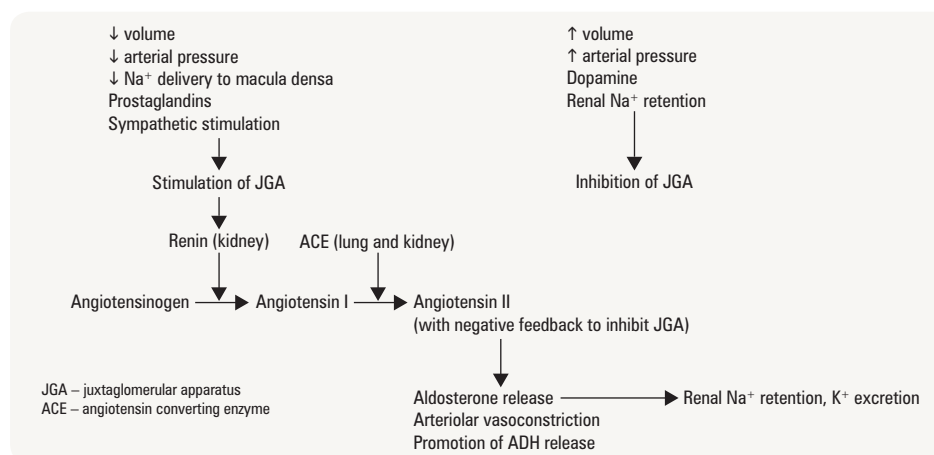


Figure 10. Renin-angiotensin-aldosterone axis (see [Nephrology](#), NP4)

## Cortisol

- a glucocorticoid, regulated by the HPA axis
- involved in regulation of metabolism; counteracts the effects of insulin
- support blood pressure, vasomotor tone
- also involved in regulation of behaviour and immunosuppression

Table 21. Physiological Effects of Glucocorticoids

Stimulatory Effects	Inhibitory Effects
Stimulate hepatic glucose production (gluconeogenesis)	Inhibit bone formation; stimulate bone resorption
Increase insulin resistance in peripheral tissues	Inhibit fibroblasts, causing collagen and connective tissue loss
Increase protein catabolism	Suppress inflammation; impair cell-mediated immunity
Stimulate leukocytosis and lymphopenia	Inhibit growth hormone axis
Increase cardiac output, vascular tone, Na <sup>+</sup> retention	Inhibit reproductive axis
Increase PTH release, urine calcium excretion	Inhibit vitamin D <sub>3</sub> and inhibit calcium uptake

## Androgens

- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age



## Layers of the Adrenal Cortex

### OUTSIDE

**Zona Glomerulosa** produces mineralocorticoids (aldosterone)

**Zona Fasciculata** produces glucocorticoids (cortisol)

**Zona Reticularis** produces androgens (DHEA, androstenedione)

### INSIDE





## Adrenocortical Functional Work-Up

### STIMULATION TEST

- purpose: diagnosis of hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

#### 1. Tests of Glucocorticoid Reserve

- Cosyntropin (ACTH analogue) Stimulation Test
  - give 1 µg or 250 µg cosyntropin IV, then measure plasma cortisol levels at time 0, 30, and 60 min
  - physiologic response: stimulated plasma cortisol of >500 nmol/L (>18 µg/dL)
  - inappropriate response: inability to stimulate increased plasma cortisol
- insulin tolerance test used to diagnose secondary or tertiary hypoadrenalism (see *Pituitary Gland*, E16)



#### Principles of Diagnosing Adrenal Disorders:

- Is the suspected hormone ↑ or ↓?
- Can it be suppressed/stimulated?
- Is the stimulating hormone ↑ or ↓? (primary vs. secondary)

### SUPPRESSION TESTS

- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

#### 1. Tests of Pituitary-Adrenal Suppressibility

- Dexamethasone (DXM) Suppression Test
  - principle: DXM suppresses pituitary ACTH → plasma cortisol should be lowered if HPA axis is normal
  - *Screening Test*: Overnight DXM Suppression Test
    - ♦ oral administration of 1 mg DXM at midnight → measure plasma cortisol levels the following day at 8 am
    - ♦ physiologic response: plasma cortisol <50 nmol/L (1.8 µg/dL), with 50-140 nmol/L being a “grey zone” (cannot be certain if normal or not)
    - ♦ inappropriate response: failure to suppress plasma cortisol
    - ♦ <20% false positive results due to obesity, depression, alcohol, other medications
  - *Confirmatory Test*: Other testing is used to confirm the diagnosis, such as:
    - ♦ 24 h urine free cortisol (shows overproduction of cortisol)
    - ♦ midnight salivary cortisol (if available), shows lack of diurnal variation
    - ♦ inappropriate response: remains high (normally will be low at midnight)

#### 2. Tests of Mineralocorticoid Suppressibility

- principle: expansion of extracellular fluid volume (ECFV) → plasma aldosterone should be lowered if HPA axis were normal
- ECFV Expansion with Normal Saline (NS)
  - IV infusion of 500 mL/h of NS for 4 h → then measure plasma aldosterone levels
  - plasma aldosterone >277 pmol/L (>10 ng/dL) is consistent with primary hyperaldosteronism, <140 pmol/L (<5 ng/dL) is normal
  - inappropriate response: failure to suppress plasma aldosterone

Mineralocorticoid Excess Syndromes

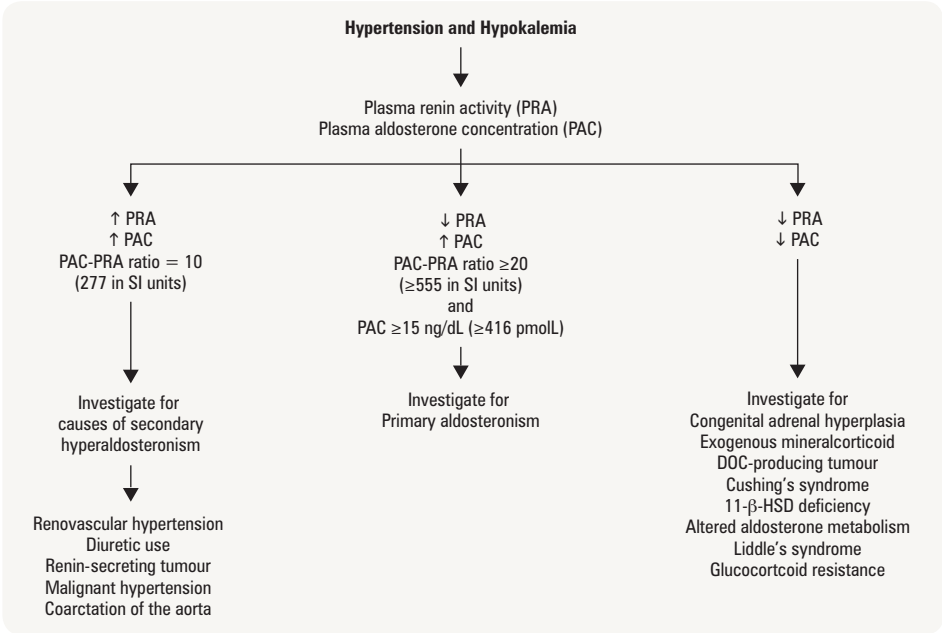


Figure 11. Approach to mineralocorticoid excess syndromes

Definition

- primary hyperaldosteronism (PH): excess aldosterone production (intra-adrenal cause)
- secondary hyperaldosteronism: aldosterone production in response to excess RAAS (extra-adrenal cause)

Etiology

- primary hyperaldosteronism
  - aldosterone-producing adrenal adenoma (Conn's syndrome)
  - bilateral or idiopathic adrenal hyperplasia
  - glucocorticoid-remediable aldosteronism)
  - aldosterone-producing adrenocortical carcinoma
  - unilateral adrenal hyperplasia
- secondary hyperaldosteronism (see Figure 11)

Clinical Features

- hypertension
- hypokalemia (may have mild hypernatremia), metabolic alkalosis
- normal K<sup>+</sup>, low Na<sup>+</sup> in SH (low effective circulating volume leads to ↑ ADH release) → edema
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, MI
- fatigue, weakness, paresthesia, headache; severe cases with tetany, intermittent paralysis

Diagnosis

- investigate plasma aldosterone to renin ratio in patients with hypertension and hypokalemia
- confirmatory testing for PH: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECFV expansion)
- imaging: CT adrenal glands

Table 22. Diagnostic Tests in Hyperaldosteronism

Test	Primary Hyperaldosteronism	Secondary Hyperaldosteronism
Plasma aldosterone to renin ratio (PAC/PRA)	Elevated (↑ aldo, ↓ renin)	Normal (↑ aldo, ↓ renin)
Salt loading test:		Not performed if normal PAC/PRA
A) Oral test:	↑ urine aldosterone	
B) IV saline test:	↑ plasma aldosterone	

Treatment

- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause

## Cushing's Syndrome

### Definition

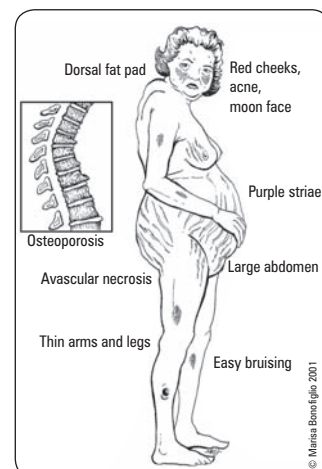
- results from chronic glucocorticoid excess (endogenous or exogenous sources)

### Etiology

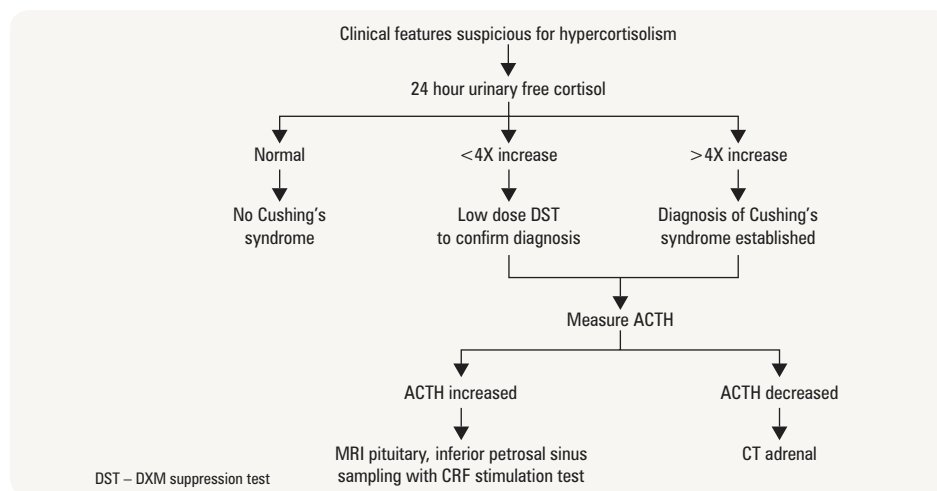
- ACTH-dependent (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
  - ACTH-secreting pituitary adenoma (Cushing's disease; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma or medullary thyroid tumours)
- ACTH-independent (15%)
  - long-term use of exogenous glucocorticoids
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia

### Clinical Features

- symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism and acne (ACTH dependent)
- signs: central obesity, round face, supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, hypertension, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism if ACTH-dependent



**Figure 12. Clinical features of Cushing's syndrome**



**Figure 13. Hypercortisolism: algorithm for diagnosis**

### Treatment

- adrenal
  - adenoma: unilateral adrenalectomy (curative)
  - carcinoma: adjunctive chemotherapy often not useful (frequent metastases, poor prognosis)
  - medical treatment: mitotane, ketoconazole to reduce cortisol
- pituitary
  - trans-sphenoidal resection, with glucocorticoid supplement post-operatively
- ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis)
  - surgical resection, if possible; chemotherapy/radiation for primary tumour
  - agents blocking adrenal steroid synthesis: metyrapone or ketoconazole

## Congenital Adrenal Hyperplasia

- see [Pediatrics](#), P31



## Hyperandrogenism

### Definition

- state of having excessive secretion of androgens (DHEA, DHEA sulfate, testosterone)

### Etiology and Pathophysiology

**Table 23. Etiology of Hyperandrogenism**

<b>Constitutional/Familial</b>	Family history, predisposing ethnic background Premature adrenarche
<b>Medications Androgen-mediated</b>	Anabolic steroids, ACTH, androgens, progestational agents
<b>Ovarian</b>	PCOS Ovarian hyperthecosis Theca cell tumours Pregnancy: placental sulfatase/aromatase deficiency
<b>Adrenal</b>	Congenital adrenal hyperplasia (CAH, late-onset CAH) Tumours (adenoma, carcinoma)
<b>Pituitary</b>	Cushing's disease – high ACTH Hyperprolactinemia

### Clinical Features

#### Females:

- hirsutism
  - male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  - Ferriman-Gallwey scoring system is used to quantify severity of hirsutism
- virilization
  - masculinization: hirsutism, temporal balding, clitoral enlargement, deepening of voice, acne
  - increase in musculature
- defeminization
  - loss of female secondary sex characteristics (i.e. amenorrhea, ↓ breast size, infertility)

#### Males:

- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in: testicular size, testicular testosterone production and spermatogenesis

### Investigations

- testosterone, DHEA-S as a measure of adrenal androgen production
- LH/FSH (commonly in PCOS >2.5)
- 17-OH progesterone, elevated in CAH due to 21-OH deficiency
- for virilization: CT/MRI of adrenals and ovaries (identify tumours)
- if PCOS, check blood glucose, lipids, 75 g OGTT

### Treatment

- discontinue causative medications
  - antiandrogens, e.g. spironolactone
- oral contraceptives (e.g. cyproterone acetate – blocks androgen receptor; found in Diane 35®)
- surgical resection of tumour
- low dose glucocorticoid ± mineralocorticoid if CAH suspected
- treat specific causative disorders, e.g. tumours, Cushing's, etc.
- cosmetic therapy (laser, electrolysis)



#### Conditions that do NOT Represent True Hirsutism

- Androgen-independent hair (e.g. lanugo hair)
- Drug-induced hypertrichosis (e.g. phenytoin, diazoxide, cyclosporine, minoxidil)
- Topical steroid use

## Adrenocortical Insufficiency

### Definition

- a state of inadequate cortisol and aldosterone production by the adrenal glands

### Etiology

#### PRIMARY (ADDISON'S DISEASE)

**Table 24. Etiology of Primary Adrenocortical Insufficiency**

<b>Autoimmune (70-90%)</b>	Isolated adrenal insufficiency Polyglandular autoimmune syndrome type I and II Antibodies often directed against adrenal enzymes and 3 cortical zones
<b>Infection</b>	TB (7-20%) (most common in developing world) Fungal: histoplasmosis, paracoccidioidomycosis HIV, CMV Syphilis African trypanosomiasis
<b>Infiltrative</b>	Metastatic cancer (lung>stomach>esophagus>colon>breast); lymphoma Sarcoidosis, amyloidosis, hemochromatosis
<b>Vascular</b>	Bilateral adrenal hemorrhage Sepsis (meningococcal, <i>Pseudomonas</i> ) Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children Thrombosis, embolism, adrenal infarction
<b>Drugs</b>	Inhibit cortisol: ketoconazole, megestrol acetate Increase cortisol metabolism: rifampin, phenytoin, barbiturates, heparin, coumadin
<b>Others</b>	Adrenoleukodystrophy Congenital adrenal hypoplasia (impaired steroidogenesis) Familial glucocorticoid deficiency or resistance

#### SECONDARY ADRENOCORTICAL INSUFFICIENCY

- inadequate pituitary ACTH secretion
- multiple etiologies (see *Hypopituitarism*, E20), including withdrawal of exogenous steroids

### Clinical Features

**Table 25. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)**

	<b>Primary AI (Addison's or Acute AI)</b>	<b>Secondary AI</b>
<b>Skin and mucosa</b>	Dark (palmar crease, extensor surface)	Pale
<b>Potassium</b>	High	Normal
<b>Sodium</b>	Low	Normal or Low
<b>Metabolic acidosis</b>	Present	Absent
<b>Associated diseases</b>	Primary hypothyroidism, Type 1 DM, vitiligo, neurological deficits	Central hypogonadism or hypothyroidism, growth hormone deficiency, diabetes insipidus, headaches, visual abnormalities
<b>Associated symptoms</b>	Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia GI: nausea, vomiting, abdominal pain, diarrhea	Same except: NO salt craving GI less common
<b>Diagnostic test</b>	Cosyntropin Stimulation Test High morning plasma ACTH	Insulin tolerance test Cosyntropin Stimulation Test Low morning plasma ACTH

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

### Treatment

- acute condition – can be life-threatening
  - IV NS in large volumes (2-3 L); add D5W if hypoglycemic from adrenal insufficiency
  - hydrocortisone 50-100 mg IV q6-8h for 24h, then gradual tapering
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-20 mg total daily dose, in 2-3 divided doses, highest dose in the AM
  - Florinef® (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
  - major stress (e.g. surgery, trauma) requires 150-300 hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection

## Adrenal Medulla

### Catecholamine Metabolism

- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine)
- broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine



#### ABC of Adrenaline

Adrenaline activates  $\beta$ -receptors, increasing Cyclic AMP

### Pheochromocytoma

#### Definition

- rare catecholamine secreting tumour derived from chromaffin cells of the sympathetic system

#### Epidemiology

- most commonly a single tumour of adrenal medulla
- rare cause of hypertension (<0.2% of all hypertensives)

#### Etiology and Pathophysiology

- most cases sporadic (80%)
- familial: associated with multiple endocrine neoplasia II (MEN IIA and IIB) (50% penetrance; i.e. 50% of people with the mutation get pheochromocytoma), von Hippel-Lindau (10-20% penetrance), paraganglioma (20% penetrance), or neurofibromatosis type 1 (0.1-5.7% penetrance)
- tumours, via unknown mechanism, able to synthesize and release excessive catecholamines

#### Clinical Features

- 50% suffer from paroxysmal HTN; the rest have sustained HTN
- classic triad: episodic "pounding" headache, palpitations/tachycardia, diaphoresis
- other symptoms: tremor, anxiety, chest or abdominal pain, nausea/vomiting, visual blurring, weight loss, polyuria, polydipsia
- other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
- symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods)

#### Investigations

- urine catecholamines
  - increased catecholamine metabolites (metanephrines) and free catecholamines
  - plasma metanephrines if available (most sensitive)
    - cut-off values will depend on assay used
- CT abdomen
  - if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

#### Treatment

- surgical removal of tumour (curative) with careful pre- and post-operative ICU monitoring
- adequate pre-operative preparation
  - $\alpha$ -blockade for BP control: phenoxybenzamine (10-21 d pre-operative), IV phentolamine (peri-operative, if required)
  - $\beta$ -blockade for HR control once  $\alpha$  blocked for a few days
  - metyrosine (catecholamine synthesis inhibitor) + phenoxybenzamine or prazosin
  - volume restoration with vigorous salt-loading and fluids
- rescreen urine 1-3 mo post-operatively
- screen urine in first degree relatives; genetic testing in patients <50 yr old



#### Pheochromocytomas 'Rule of 10s'

10% extra-adrenal  
10% bilateral  
10% malignant  
10% familial



#### Classic Triad of PHEochromocytoma

Palpitations  
Headache  
Episodic sweating

## Disorders of Multiple Endocrine Glands

### Multiple Endocrine Neoplasm (MEN)

- neoplastic syndromes involving multiple endocrine glands
- tumours of neuroectodermal origin
- autosomal dominant inheritance with variable penetrance
- genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit in MEN II
  - early cure and prevention of medullary thyroid cancer



**Table 26. MEN Classification**

Type	Tissues Involved	Clinical Manifestations
<b>MEN I (chromosome 11)</b>		
<b>Wermer's Syndrome</b>	Pituitary Ant. pituitary adenoma	Headache, visual field defects. Often non-secreting but may secrete GH (acromegaly) and PRL (galactorrhea, erectile dysfunction, decreased libido, amenorrhea)
	Parathyroid Primary hyperparathyroidism from hyperplasia	Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcemia
	Entero-pancreatic endocrine Pancreatic islet cell tumours	Epigastric pain (peptic ulcers and esophagitis)
	Gastrinoma	Hypoglycemia
	Insulinomas	Secretory diarrhea
	Vasoactive intestinal peptide (VIP)-omas	
	Glucagonoma	Rash, anorexia, anemia, diarrhea, glossitis
	Carcinoid syndrome	Flushing, diarrhea, bronchospasm
<b>MEN II (chromosome 10)</b>		
<b>1. IIa Sipple's Syndrome</b>	Thyroid (>90%) Medullary thyroid cancer (MTC)	Physical signs are variable and often subtle
	Adrenal medulla (40-50%) Pheochromocytoma	Neck mass or thyroid nodule; non-tender, anterior lymph nodes HTN, palpitations, headache, sweating
	Parathyroid (10-20%) 1° parathyroid hyperplasia	Symptoms of hypercalcemia
	Skin Cutaneous lichen amyloidosis	Scaly skin rash
<b>2. Familial Medullary Thyroid Ca (a variant of IIa)</b>	Thyroid MTC	MTC without other clinical manifestations of MEN IIa or IIb
<b>3. IIb</b>	Thyroid MTC	MTC: most common component, more aggressive and earlier onset than MEN IIa
	Adrenal medulla Pheochromocytoma	HTN, palpitations, headache, sweating
	Neurons Mucosal neuroma, intestinal ganglioneuromas	Chronic constipation; megacolon
	MSK	Marfanoid habitus (no aortic abnormalities)



**MEN I – Wermer's Syndrome Affects the 3 Ps**

Pituitary  
Parathyroid  
Pancreas

## Investigations

- MEN I
  - laboratory
    - ♦ may consider genetic screening for MEN-1 mutation in index patients
      - if a mutation is identified, screen family members who are at risk
    - ♦ gastrinoma: elevated serum gastrin level (>200 ng/mL) after IV injection of secretin
    - ♦ insulinoma: reduced fasting blood glucose (hypoglycemia) with elevated insulin and C-peptide levels
    - ♦ glucagonoma: elevated blood glucose and glucagon levels
    - ♦ pituitary tumours: assess GH, IGF-1 and prolactin levels (for over-production), TSH, free T<sub>4</sub>, 8 AM cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)
    - ♦ hyperparathyroidism: serum Ca<sup>2+</sup> and albumin, PTH levels; bone density scan (DEXA)
  - imaging
    - ♦ MRI for pituitary tumours, gastrinoma, insulinoma
- MEN II
  - laboratory
    - ♦ genetic screening for RET mutations in all index patients
      - if a mutation is identified screen family members who are at risk
    - ♦ calcitonin levels (MTC); urine catecholamines and metanephrines (pheochromocytoma); serum Ca<sup>2+</sup>, albumin and PTH levels (hyperparathyroidism)
    - ♦ pentagastrin ± calcium stimulation test if calcitonin level is within reference range
    - ♦ FNA for thyroid nodules → cytology
  - imaging
    - ♦ CT or MRI of adrenal glands, metaiodobenzylguanidine (MIBG) scan for pheochromocytoma
    - ♦ octreoscan and/or radionuclide scanning for determining the extent of metastasis

## Treatment

- MEN I
  - medical
    - ♦ proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - ♦ cabergoline or other dopamine agonists to suppress prolactin secretion
    - ♦ somatostatin for symptomatic carcinoid tumours

- surgery for hyperparathyroidism, insulinoma, glucagonoma, pituitary tumours (if medical treatment fails for the latter)
  - ♦ trans-sphenoidal approach with prn external radiation
- MEN II
  - surgery for MEN IIa with pre-operative medical therapy:
    - ♦ prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
    - ♦  $\alpha$ -blocker for at least 10-21 d for pheochromocytoma pre-op
    - ♦ hydration, calcitonin, IV bisphosphonates for hypercalcemia

## Calcium Homeostasis

- normal total serum  $\text{Ca}^{2+}$ : 2.2-2.6 mmol/L (8.5-10.5 mg/dL)
- ionic/free  $\text{Ca}^{2+}$  levels: 1.15-1.31 mmol/L (4.6-5.25 mg/dL)
- serum  $\text{Ca}^{2+}$  is about 50% protein bound (mostly albumin)
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D
- actions mainly on three organs: GI tract, bone, and kidney

**Table 27. Major Regulators in Calcium Homeostasis**

Major Regulators	Source	Regulation	Net Effect
PTH	Parathyroid glands	Stimulated by low serum $\text{Ca}^{2+}$ and high serum $\text{PO}_4^{3-}$ ; inhibited by chronic low serum $\text{Mg}^{2+}$ , high serum $\text{Ca}^{2+}$ , and calcitriol	$\uparrow \text{Ca}^{2+}$ $\uparrow \text{Calcitriol}$ $\downarrow \text{PO}_4^{3-}$
Calcitriol (1,25-(OH) $_2\text{D}_3$ )	Dietary intake Synthesized from cholesterol: UV on skin makes cholecalciferol (VitD $_3$ ) $\rightarrow$ liver makes calcidiol (25-(OH)D $_3$ ) $\rightarrow$ kidneys make calcitriol	Renal calcitriol production is stimulated by low serum $\text{PO}_4^{3-}$ and PTH; inhibited by high serum $\text{PO}_4^{3-}$ and calcitriol in negative feedback	$\uparrow \text{Ca}^{2+}$ $\uparrow \text{PO}_4^{3-}$
Calcitonin	Thyroid C cells	Stimulated by pentagastrin (GI hormone) and high serum $\text{Ca}^{2+}$ ; inhibited by low serum $\text{Ca}^{2+}$	$\downarrow \text{Ca}^{2+}$ (in pharmacologic doses) $\downarrow \text{PO}_4^{3-}$
$\text{Mg}^{2+}$	Major intracellular divalent cation	See section on <i>Magnesium</i> (E42)	Cofactor for PTH secretion
$\text{PO}_4^{3-}$	Intracellular anion found in all tissues	See section on <i>Phosphate</i> (E41)	$\downarrow \text{Ca}^{2+}$



**Pseudohypercalcemia:** increased protein binding leading to an elevation in serum total  $\text{Ca}^{2+}$  without a rise in the ionized/free form, e.g. hyperalbuminemia from severe dehydration.



**Primary Hyperparathyroidism:** Increased PTH secretion commonly due to parathyroid adenoma, lithium therapy; less often parathyroid carcinoma or parathyroid hyperplasia

**Secondary Hyperparathyroidism:** Partial resistance to PTH action leads to parathyroid gland hyperplasia and increased PTH secretion, often in patients with renal failure and osteomalacia. Due to low or low normal serum calcium levels

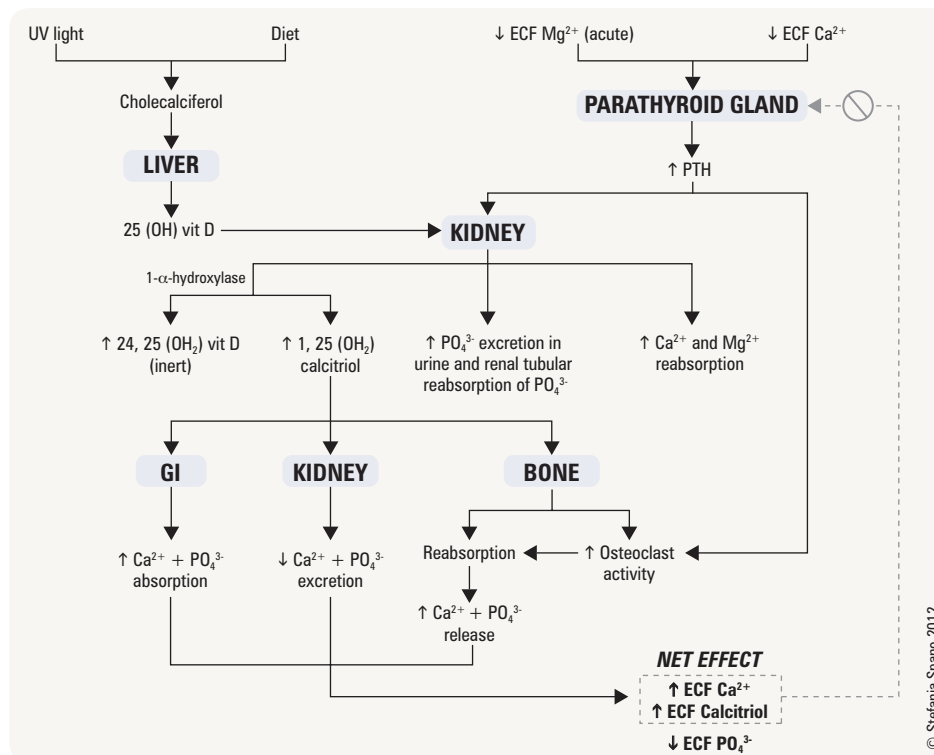
**Tertiary Hyperparathyroidism:** Irreversible clonal outgrowth of parathyroid glands, usually in long-standing inadequately treated chronic renal failure on dialysis



**Primary Hyperparathyroidism** is the most common cause of hypercalcemia in healthy outpatients. Most commonly related to a solitary adenoma or less commonly multiple gland hyperplasia. Surgical excision acts as a definitive treatment and is recommended for patients who are symptomatic. For mild asymptomatic disease medial surveillance may be appropriate with annual serum calcium, creatinine, and BMD.

**For asymptomatic patients surgery is recommended for those who meet  $\geq 1$  of the following criteria:**

- Serum calcium concentration more than 0.25 mmol/L (1.0 mg/dL) above the upper limit of normal
- Creatinine clearance  $< 60$  mL/min
- BMD T-score  $< -2.5$  at hip, spine, or distal radius, and/or previous fragility fracture
- Age  $< 50$  yr



© Stefania Spano 2012

**Figure 14. Parathyroid hormone (PTH) regulation**

## Hypercalcemia

### Definition

- total corrected serum  $\text{Ca}^{2+} > 2.6 \text{ mmol/L}$  (10.5 mg/dL) OR ionized  $\text{Ca}^{2+} > 1.35 \text{ mmol/L}$  (5.4 mg/dL)

### Approach to Hypercalcemia (Figure 15)

1. Is the patient hypercalcemic? (correct for albumin – see sidebar)
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low? If phosphate is high/normal is the level of vitamin D metabolites high or low?

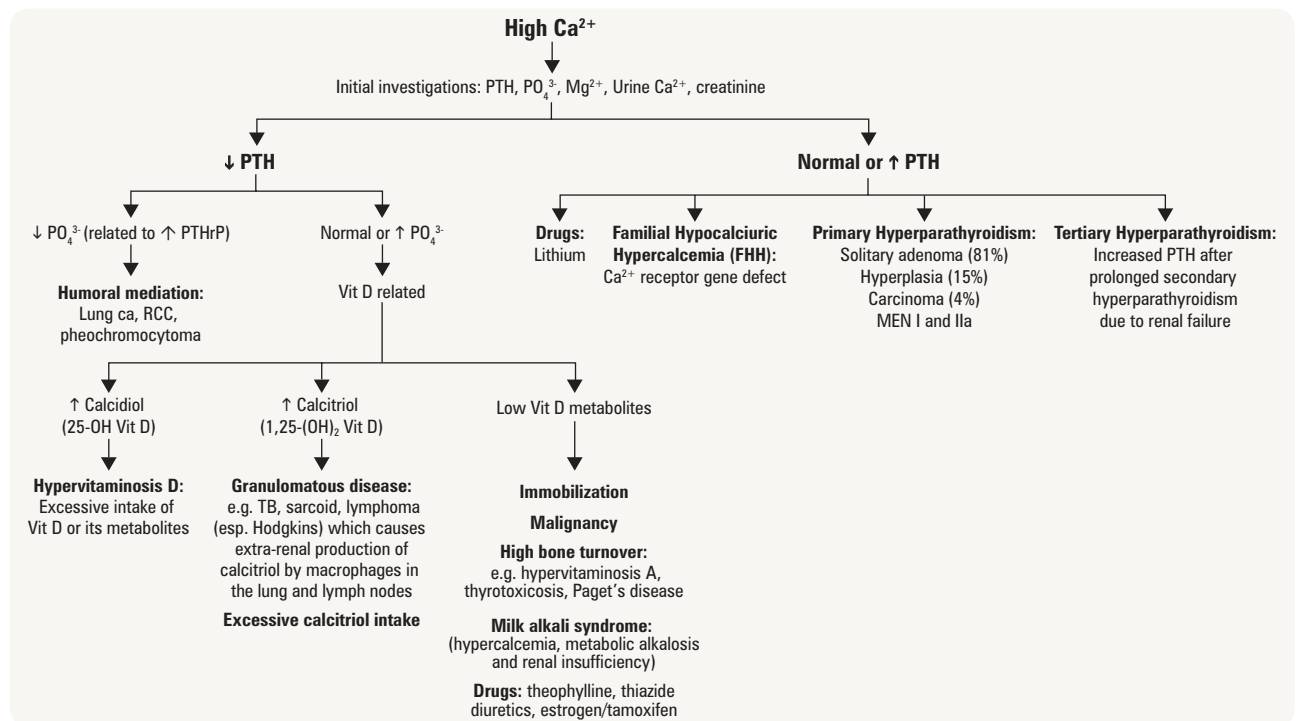


Figure 15. Differential diagnosis of hypercalcemia

### Clinical Features

- symptoms depend on the absolute  $\text{Ca}^{2+}$  value and the rate of its rise (may be asymptomatic)

Table 28. Symptoms of Hypercalcemia

Cardiovascular	GI	Renal	Rheumatological	MSK	Psychiatric	Neurologic
Hypertension Arrhythmia Short QT Deposition of $\text{Ca}^{2+}$ on valves, coronary arteries, myocardial fibres	Constipation Anorexia Nausea Vomiting (groans) PUD pancreatitis	Polyuria (Nephrogenic DI) Polydipsia Nephrolithiasis (stones) Renal failure (irreversible)	Gout Pseudogout Chondrocalcinosis	Weakness Bone pain (bones)	$> 3 \text{ mmol/L}$ (12 mg/dL) Increased alertness Anxiety Depression Cognitive dysfunction Organic brain syndromes $> 4 \text{ mmol/L}$ (16 mg/dL) Psychosis (moans)	Hypotonia Hyporeflexia Myopathy Paresis

**\*\* Hypercalcemic crisis (usually  $> 4 \text{ mmol/L}$  or  $16 \text{ mg/dL}$ ):** primary symptoms include oliguria/anuria and mental status changes (including somnolence and eventually coma) → this is a medical emergency and should be treated immediately!

### Treatment

- treatment depends on the  $\text{Ca}^{2+}$  level and the symptoms
- treat acute, symptomatic hypercalcemia aggressively



Corrected  $\text{Ca}^{2+}$  (mmol/L) = measured  $\text{Ca}^{2+} + 0.02 (40 - \text{albumin})$

For every decrease in albumin by 10, increase in  $\text{Ca}^{2+}$  by 0.2

Benign (less likely malignant):  
 $\text{Ca}^{2+} < 2.75 \text{ mmol/L}$  (11 mg/dL)

Pathologic (more likely malignant):  
 $\text{Ca}^{2+} > 3.25 \text{ mmol/L}$  (13 mg/dL)



The symptoms and signs of hypercalcemia include:  
"Bones, stones, groans and psychic overtones"



The most common cause of hypercalcemia in hospital is malignancy-associated hypercalcemia

- Usually occurs in the later stages of disease
- Most commonly seen in lung, renal, breast, ovarian and squamous tumours, as well as lymphoma and multiple myeloma

#### Mechanisms:

- Secretion of parathyroid hormone-related protein (PTHrP) which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption
- Cytokines in multiple myeloma
- Calcitriol production by lymphoma (1-hydroxylates 25, OH-vitamin D)
- Osteolytic bone metastases direct effect
- Excess PTH in Parathyroid CA

**Table 29. Treatment of Acute Hypercalcemia/Hypercalcemic Crisis**

<b>Increase Urinary <math>\text{Ca}^{2+}</math> Excretion</b>	Isotonic saline (4-5 L) over 24 h $\pm$ loop diuretic (e.g. furosemide) but only if hypervolemic Calcitonin: <ul style="list-style-type: none"> <li>• 4 IU/kg IM/SC q12h</li> <li>• 8 IU/kg IM/SC q6h</li> <li>• Only works for 48 h</li> <li>• Rapid onset within 4-6 h</li> </ul>
<b>Diminish Bone Resorption</b>	Bisphosphonates (Tx of choice) <ul style="list-style-type: none"> <li>• Inhibits osteoclastic bone resorption and promotes renal excretion of calcium</li> <li>• Acts rapidly but often transient response (decreased by 0.3-0.5 mmol/L (1.2-2.0 mg/dL) beginning within 4-6 h) max effect usually in 7 d</li> <li>• Combination of calcitonin and steroids may prolong reduction in calcium</li> <li>• Tachyphylaxis may occur</li> <li>• Indicated in malignancy-related hypercalcemia (IV pamidronate is most commonly used, zoledronic acid also now used in CA patient)</li> </ul> Mithramycin (rarely used) – effective when patient cannot tolerate large fluid load <ul style="list-style-type: none"> <li>• Dangerous – hematotoxic and hepatotoxic</li> </ul>
<b>Decrease GI <math>\text{Ca}^{2+}</math> Absorption</b>	Corticosteroids in hypervitaminosis D and hematologic malignancies <ul style="list-style-type: none"> <li>• Anti-tumour effects <math>\rightarrow</math> decreased calcitriol production by the activated mononuclear cells in lung and lymph node</li> <li>• Slow to act (5-10 d); need high dose</li> </ul>
<b>Dialysis</b>	Treatment of last resort <ul style="list-style-type: none"> <li>• Indication: severe malignancy-associated hypercalcemia and renal insufficiency or heart failure</li> </ul>

**Differential Diagnosis of Hypercalcemia**

- **Primary hyperparathyroidism**
- **Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2)**
- Renal disease: tertiary hyperparathyroidism
- Drugs: calcium carbonate, milk-alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication
- Familial hypocalciuric hypercalcemia
- Granulomatous disease: sarcoidosis, TB, Hodgkin's lymphoma
- Thyroid disease: thyrotoxicosis
- Adrenal disease: adrenal insufficiency, pheochromocytoma
- Immobilization

**Watch Out For:**

- Volume depletion via diuresis
- Arrhythmias

**Acute Management of Hypercalcemia/Hypercalcemic Crisis**

- Volume expansion (e.g. NS IV 300-500 cc/h): initial therapy
- Calcitonin: transient, partial response
- Bisphosphonate: treatment of choice
- Corticosteroid: most useful in Vit D toxicity, granulomatous disease, some malignancies
- Saline diuresis + loop diuretic (for volume overload): temporary measure



Hypomagnesemia can impair PTH secretion and action.

**Differential Diagnosis of Tetany**

- Hypocalcemia
- Metabolic alkalosis (with hyperventilation)
- Hypokalemia
- Hypomagnesemia

**Signs and Symptoms of Acute Hypocalcemia**

- **Paresthesias:** perioral, hands and feet
- **Chvostek's sign:** percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles
- **Trousseau's sign:** inflation of a blood pressure cuff above systolic pressure for 3 min elicits carpal spasm and paresthesia

## Hypocalcemia

**Definition**

- total corrected serum  $\text{Ca}^{2+}$  <2.2 mmol/L (8.5 mg/dL)

**Table 30. Clinical Features of Hypocalcemia**

Acute Hypocalcemia	Chronic Hypocalcemia
Paresthesia	CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson's, dystonia, hemiballismus, papilledema, pseudotumour cerebri
Laryngospasm (with stridor)	CVS: prolonged QT interval $\rightarrow$ Torsades de pointes (ventricular tachycardia)
Hyperreflexia	GI: steatorrhea
Tetany	ENDO: impaired insulin release
Chvostek's sign (tap CN VII)	SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition
Trousseau's sign (carpal spasm)	OCULAR: cataracts
ECG changes	MSK: generalized muscle weakness and wasting
Delirium	
Psychiatric Sx: emotional instability, anxiety and depression	

**Approach to Hypocalcemia (Figure 16)**

1. Is the patient hypocalcemic?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?
4. Is the  $\text{Mg}^{2+}$  level low?

**Approach to Treatment**

- correct underlying disorder
- mild/asymptomatic (ionized  $\text{Ca}^{2+}$  >0.8 mmol/L, 3.2 mg/dL)
  - treat by increasing dietary  $\text{Ca}^{2+}$  by 1000 mg/d
  - calcitriol 0.25  $\mu\text{g}/\text{d}$
- acute/symptomatic hypocalcemia (ionized  $\text{Ca}^{2+}$  <0.7 mmol/L, 2.8 mg/dL)
  - immediate treatment required
  - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion if necessary
  - goal is to raise  $\text{Ca}^{2+}$  to low normal range (2.0-2.1 mmol/L, 8.0-8.4 mg/dL) to prevent symptoms but allow maximum stimulation of PTH secretion
- if PTH recovery not expected, requires long-term therapy with calcitriol and calcium
- **do not correct hypocalcemia if asymptomatic and suspected to be transient**

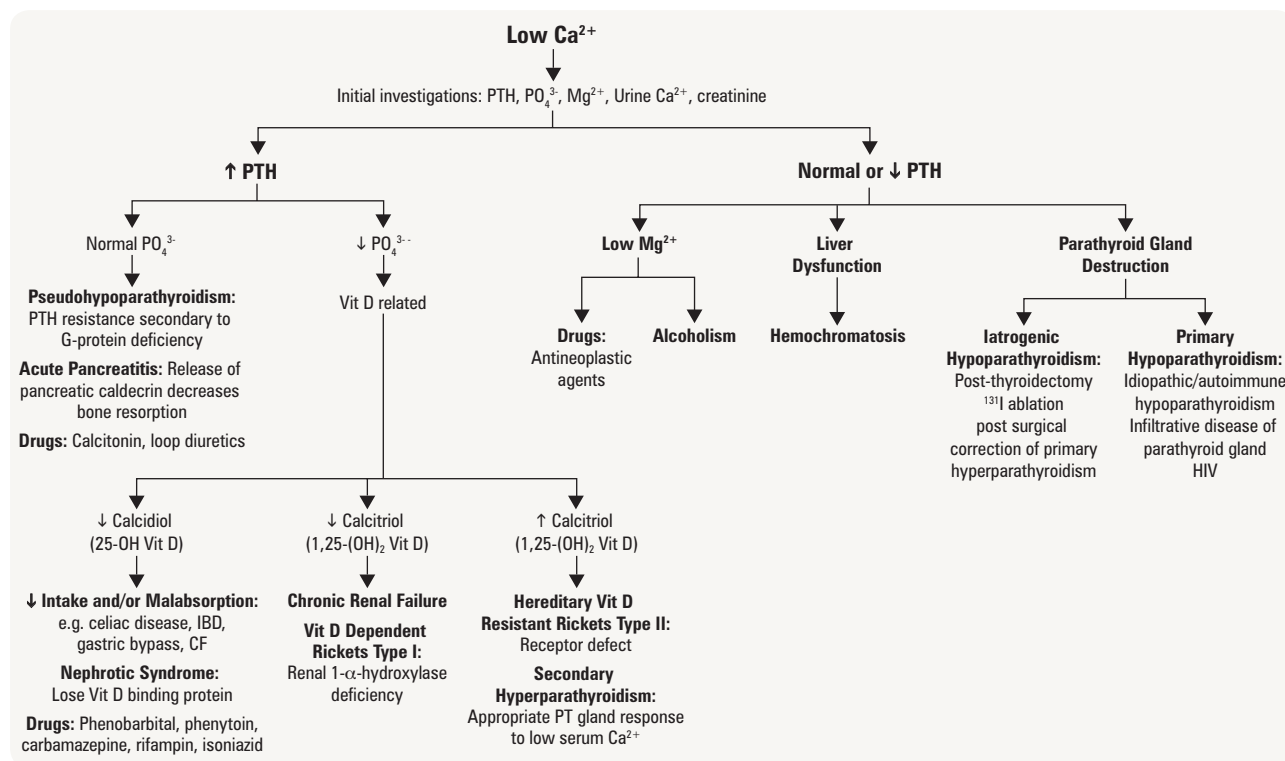


Figure 16. Etiology and clinical approach to hypocalcemia

## Hyperphosphatemia

### Definition

- serum phosphate  $>1.45$  mmol/L (4.1 mg/dL)

Table 31. Etiology of Hyperphosphatemia

Increased Phosphate Load	Reduced Renal Clearance	Pseudohyperphosphatemia
GI intake (rectal enema, GI bleeding) IV phosphate load (K-Phos®, blood transfusion) Endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis, lactic and ketoacidosis)	Acute/chronic renal failure Hypoparathyroidism Acromegaly Tumour calcinosis (ability of kidney to specifically clear phosphate is defective)	Hyperglobulinemia Hyperlipidemia Hyperbilirubinemia

### Clinical Features

- non-specific, include ectopic calcification, renal osteodystrophy

### Treatment

- acute: hemodialysis if symptomatic
- chronic: low  $\text{PO}_4^{3-}$  diet, phosphate binders (e.g.  $\text{CaCO}_3$ )

## Hypophosphatemia

### Definition

- serum phosphate  $<0.85$  mmol/L (2.4 mg/dL)

Table 32. Etiology of Hypophosphatemia

Inadequate Intake	Renal Losses	Excessive Skeletal Mineralization	Shift into ICF
Starvation Malabsorption (diarrhea, steatorrhea) Antacid use Alcoholism	Hyperparathyroidism Diuretics X-linked or AD hypophosphatemic rickets Fanconi syndrome Multiple myeloma	Osteoblastic metastases Post parathyroidectomy (referred to as 'hungry bone syndrome')	Recovery from metabolic acidosis Respiratory alkalosis Starvation refeeding (stimulated by insulin)



Symptoms usually present when phosphate  $<0.32$  mmol/L (1.0 mg/dL)  
Treat asymptomatic patients if phosphate  $<0.64$  mmol/L (2.0 mg/dL)

**Clinical Features**

- non-specific (CHF, coma, hypotension, weakness, defective clotting)

**Treatment**

- treat underlying cause
  - Oral  $\text{PO}_4^{3-}$ : 2-4 g/d divided bid-qid (start at 1 g/d to minimize diarrhea)
  - IV  $\text{PO}_4^{3-}$ : only for severely symptomatic patients or inability to tolerate oral therapy

**Hypermagnesemia****Definition**

- serum magnesium  $>0.85$  mmol/L (2.1 mg/dL)

**Etiology**

- AKI/CRF
- $\text{Mg}^{2+}$ -containing antacids or enemas
- IV administration of large doses of  $\text{MgSO}_4$  (e.g. for preeclampsia; see [Obstetrics](#), OB16)

**Clinical Features**

- drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest

**Treatment**

- discontinue  $\text{Mg}^{2+}$ -containing products
- IV calcium ( $\text{Mg}^{2+}$ -antagonist) for acute reversal of magnesium toxicity
- dialysis if renal failure

**Hypomagnesemia****Definition**

- serum magnesium  $<0.70$  mmol/L (1.7 mg/dL)

**Etiology**

- GI losses
  - starvation/malabsorption
  - vomiting/diarrhea
  - alcoholism
  - acute pancreatitis
- excess renal loss
  - $2^\circ$  hyperaldosteronism due to cirrhosis and CHF
  - hyperglycemia
  - hypokalemia
  - hypercalcemia
  - loop and thiazide-type diuretics
  - nephrotoxic medications
  - proton-pump inhibitors

**Clinical Features**

- seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities) and arrhythmias including Torsades de pointes

**Treatment**

- treat underlying cause
- $\text{Mg}^{2+}$  IM/IV; cellular uptake of  $\text{Mg}^{2+}$  is slow, therefore repletion requires sustained correction
- discontinue diuretics
  - in patients requiring diuretics, use a  $\text{K}^+$ -sparing diuretic to minimize magnesuria



You will be unable to correct hypokalemia or hypocalcemia without first supplementing magnesium if patient hypomagnesemic.

**Metabolic Bone Disease****Osteoporosis****Definition**

- a condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture
- bone mineral density (BMD)  $\geq 2.5$  standard deviations below the peak bone mass for young adults (i.e. T-score  $\leq -2.5$ )
- osteopenia: BMD with T-score between -1.0 and -2.5

**ETIOLOGY AND PATHOPHYSIOLOGY****Primary Osteoporosis**

- primary type 1: most common in post-menopausal women, due to decline in estrogen, worsens with age
- primary type 2: occurs after age 75, seen in females and males at 2:1 ratio, possibly due to zinc deficiency



## Secondary Osteoporosis

- gastrointestinal diseases
  - gastrectomy
  - malabsorption (e.g. celiac disease)
  - chronic liver disease
- bone marrow disorders
  - multiple myeloma
  - lymphoma
  - leukemia
- endocrinopathies
  - Cushing's syndrome
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - diabetes
- malignancy
  - secondary to chemotherapy
  - myeloma
- drugs
  - corticosteroid therapy
  - phenytoin
  - chronic heparin therapy
  - androgen deprivation therapy
  - aromatase inhibitors
- other
  - rheumatologic disorders
    - ♦ rheumatoid arthritis
    - ♦ SLE
    - ♦ ankylosing spondylitis
  - renal disease
  - poor nutrition
  - immobilization

## Clinical Features

- commonly asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus and wrist
  - fragility fractures: fracture with fall from standing height
  - Dowager's hump: collapse fracture of vertebral bodies in mid-dorsal region
  - x-ray: vertebral compression and crush fractures, wedge fractures, "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
- pain, especially backache, associated with fractures

## Approach to Osteoporosis

1. Assess risk factors for osteoporosis on history and physical
2. Decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women  $\geq 65$  yr or younger if presence of risk factors (Table 33)
3. Initial investigations:
  - all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
  - also consider serum and urine protein electrophoresis, celiac workup and 24 h urinary  $\text{Ca}^{2+}$  excretion to rule out additional secondary causes
  - **25-OH-Vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level  $\geq 75$  nmol/L is achieved**
  - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture
4. Assess 10-yr fracture risk by combining BMD result and risk factors (only if  $\geq 50$  yr)
  - 1) WHO Fracture Risk Assessment Tool (FRAX);
  - 2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
    - ♦ approach to management guided by 10-yr risk stratification into low, medium, high risk
5. For all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see Table 35)

**Table 33. Osteoporosis Risk Stratification**

<b>Low Risk</b> 10-yr fracture risk <10%	Unlikely to benefit from pharmacotherapy; encourage lifestyle changes Reassess risk in 5 yr
<b>Medium Risk</b> 10-yr fracture risk 10-20%	Discuss patient preference for management and consider additional risk factors Factors that warrant consideration for pharmacological therapy: <ul style="list-style-type: none"> <li>• Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray</li> <li>• Previous wrist fracture in individuals <math>\geq 65</math> or with T-score <math>\leq -2.5</math></li> <li>• Lumbar spine T-score much lower than femoral neck T-score</li> <li>• Rapid bone loss</li> <li>• Men receiving androgen-deprivation therapy for prostate cancer</li> <li>• Women receiving aromatase-inhibitor therapy for breast cancer</li> <li>• Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use</li> <li>• Recurrent falls (defined as falling 2 or more times in the past 12 mo)</li> <li>• Other disorders strongly associated with osteoporosis</li> </ul> Repeat BMD and reassess risk every 1-3 yr initially
<b>High Risk</b> 10-yr fracture risk >20%; OR Prior fragility fracture of hip or spine; OR More than one fragility fracture	Start pharmacotherapy



**Corticosteroid Therapy is a Common Cause of Secondary Osteoporosis**  
 Individuals receiving  $\geq 7.5$  mg of prednisone daily for over 3 mo should be assessed for bone-sparing therapy  
 Mechanism: increased resorption + decreased formation



**Use of Calcium or Calcium in Combination with Vitamin D Supplementation to Prevent Fractures and Bone Loss in People Aged 50 Years and Older: A Meta-Analysis**

*Lancet* 2007;370:657-666

**Purpose:** To determine whether supplementation with calcium or calcium in combination with vitamin D reduces fractures of all types and percentage change of bone-mineral density from baseline.

**Study Selection:** RCTs that recruited people aged 50 yr or older.

**Results:** In trials that reported fracture as an outcome (17 trials,  $n=52,625$ ), treatment was associated with a 12% risk reduction in fractures of all types (risk ratio 0.88, 95% CI 0.83-0.95;  $p=0.0004$ ). In trials that reported bone-mineral density as an outcome (23 trials,  $n=41,419$ ), the treatment was associated with a reduced rate of bone loss of 0.54% (0.35-0.73;  $p<0.0001$ ) at the hip and 1.19% (0.76-1.61%;  $p<0.0001$ ) in the spine. The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high ( $p<0.0001$ ). The treatment effect was better with calcium doses of 1200 mg or more (0.80 vs. 0.94;  $p=0.006$ ), and with vitamin D doses of 800 IU or more (0.84 vs. 0.87;  $p=0.03$ ).

**Conclusion:** Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 yr or older. For best therapeutic effect, use doses of 1200 mg of calcium, and 800 IU of vitamin D.

Table 34. Indications for BMD Testing

Older Adults (age $\geq 50$ yr)	Younger Adults (age $< 50$ yr)
<p>All women and men age <math>\geq 65</math> yr</p> <p>Menopausal women, and men aged 50-64 yr with clinical risk factors for fracture:</p> <ul style="list-style-type: none"> <li>• Fragility fracture after age 40</li> <li>• Prolonged glucocorticoid use</li> <li>• Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy)</li> <li>• Parental hip fracture</li> <li>• Vertebral fracture or osteopenia identified on x-ray</li> <li>• Current smoking</li> <li>• High alcohol intake</li> <li>• Low body weight (<math>&lt; 60</math> kg) or major weight loss (<math>&gt; 10\%</math> of weight at age 25 yr)</li> <li>• Rheumatoid arthritis</li> <li>• Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, Type 1 diabetes, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<math>&lt; 45</math> yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g. inflammatory bowel disease)</li> </ul>	<p>Fragility fracture</p> <ul style="list-style-type: none"> <li>• Prolonged use of glucocorticoids</li> <li>• Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy)</li> <li>• Hypogonadism or premature menopause</li> <li>• Malabsorption syndrome</li> <li>• Primary hyperparathyroidism</li> <li>• Other disorders strongly associated with rapid bone loss and/or fracture</li> </ul>

## Treatment of Osteoporosis

Table 35. Treatment of Osteoporosis in Women and Men

Treatment for both men and women	
<b>Lifestyle</b>	<p>Diet: Elemental calcium 1000-1200 mg/d; Vit D 1000 IU/d</p> <p>Exercise: 3x30 min weight-bearing exercises/wk</p> <p>Cessation of smoking, reduce caffeine intake</p> <p>Stop/avoid osteoporosis-inducing medications</p>
<b>Drug Therapy</b>	
<b>Bisphosphonate:</b> Inhibitors of osteoclast binding	<p>1st line in prevention of hip, nonvertebral and vertebral # (Grade A): alendronate, risedronate, zoledronic acid</p> <p>2nd line (Grade B): etidronate</p>
<b>RANKL inhibitors</b>	Denosumab: 1st line in prevention of hip, nonvertebral, vertebral # (Grade A)
<b>Parathyroid Hormone</b>	YES fragility #: 18-24 mo duration
<b>Calcitonin (2nd line):</b> osteoclast receptor binding	YES fragility #: Calcitonin 200 IU nasally OD with Calcitriol 0.25 $\mu$ g bid
Treatment specific to post-menopausal women	
<b>SERM (selective estrogen-receptor modulator):</b> agonistic effect on bone but antagonistic effect on uterus and breast	<p>Raloxifene: 1st line in prevention of vertebral # (Grade A)</p> <ul style="list-style-type: none"> <li>• +ve: prevents osteoporotic # (Grade A to B evidence), improves lipid profile, decreased breast ca risk</li> <li>• -ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps</li> </ul>
<b>HRT:</b> combined estrogen + progesterone (see <a href="#">Gynecology</a> , GY33)	<p>1st line in prevention of hip, nonvertebral and vertebral # (Grade A)</p> <p>For most women, risks <math>&gt;</math> benefits</p> <ul style="list-style-type: none"> <li>• Combined estrogen/progestin prevents hip, vertebral, total #</li> <li>• Increased risks of breast ca, cardiovascular events and DVT/PE</li> </ul>

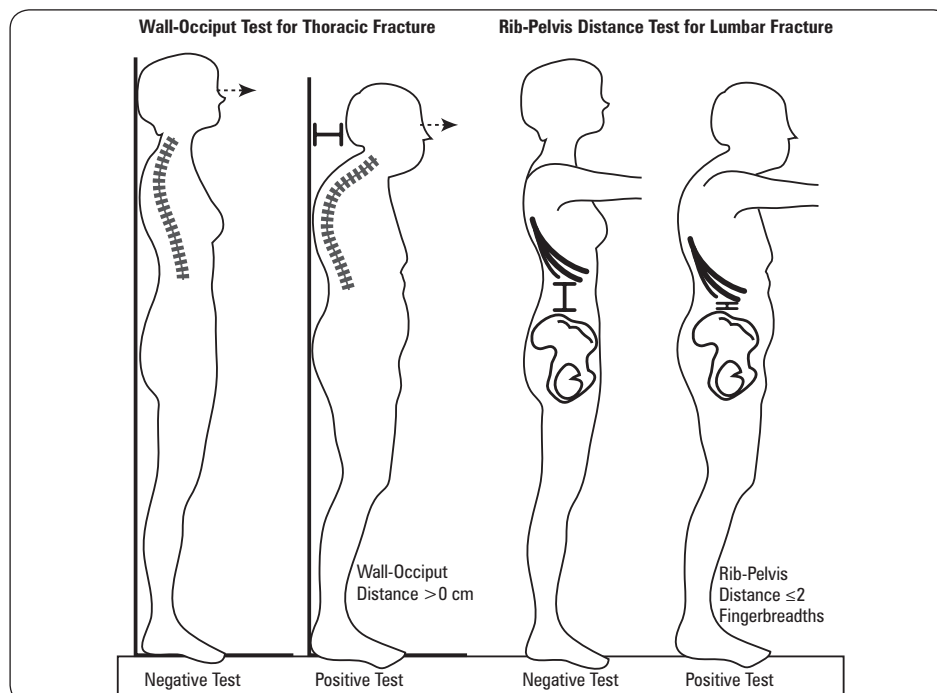


Figure 17. Physical examination test



### Clinical Signs of Fractures or Osteoporosis

- Height loss  $> 3$  cm (Sn 92%)
- Weight  $< 51$  kg
- Kyphosis (Sp 92%)
- Tooth count  $< 20$  (Sp 92%)
- Grip strength
- Armspan-height difference  $> 5$  cm (Sp 76%)
- Wall-occiput distance  $> 0$  cm (Sp 87%)
- Rib-pelvis distance  $\leq 2$  finger breadth (Sn 88%)



### Alendronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women

Cochrane DB Syst Rev 2008;1:CD001155

### Etidronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women

Cochrane Database Syst Rev. 2008;(1):CD003376

### Risedronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women

Cochrane Database Syst Rev. 2008;(1):CD004523

**Purpose:** To assess the efficacy of three bisphosphonates in the primary and secondary prevention of osteoporotic fractures in postmenopausal women.

**Study Selection:** Women receiving at least one yr of bisphosphonates for postmenopausal osteoporosis were compared to those receiving placebo or concurrent calcium/vitamin D or both. The outcome was fracture incidence.

**Results:** Levels of evidence: <http://www.cochranemsk.org/review/writing/>  
%RRR and %ARR for 5 yr fracture incidence reduction.

#### Alendronate (10 mg/d)

1° Prevention – Vertebral 45% RRR, 2% ARR (Gold)

1° Prevention – Hip Not significant

1° Prevention – Wrist Not significant

2° Prevention – Vertebral 45% RRR, 6% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

2° Prevention – Wrist 50% RRR, 2% ARR (Gold)

2° Prevention – Hip 53% RRR, 1% ARR (Gold)

## Osteomalacia and Rickets

- **rickets:** osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *prior* to epiphyseal closure (in childhood)
- **osteomalacia:** osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *after* epiphyseal closure (in adulthood)

### Etiology and Pathophysiology

#### Vitamin D Deficiency

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy
- loss of vitamin D binding protein
  - nephrotic syndrome
- defective 1- $\alpha$ -25 hydroxylation
  - hypoparathyroidism
  - renal failure
- pathophysiology: leads to secondary hyperparathyroidism and hypophosphatemia

#### Mineralization Defect

- abnormal matrix
  - osteogenesis imperfecta
  - fibrogenesis imperfecta
  - axial osteomalacia
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - bisphosphonates, aluminum, high dose fluoride, anticonvulsants



#### Factors Necessary for Mineralization

- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

**Table 36. Clinical Presentations of Rickets and Osteomalacia**

Rickets	Osteomalacia
<ul style="list-style-type: none"> <li>• Skeletal pain and deformities, bow legged</li> <li>• Fracture susceptibility</li> <li>• Weakness and hypotonia</li> <li>• Disturbed growth</li> <li>• Ricketic rosary (prominent costochondral junctions)</li> <li>• Harrison's groove (indentation of lower ribs)</li> <li>• Hypocalcemia</li> </ul>	<ul style="list-style-type: none"> <li>• Not as dramatic</li> <li>• Diffuse skeletal pain</li> <li>• Bone tenderness</li> <li>• Fractures</li> <li>• Gait disturbances (waddling)</li> <li>• Proximal muscle weakness</li> <li>• Hypotonia</li> </ul>

### Investigations

**Table 37. Laboratory Findings in Osteomalacia and Rickets**

Disorder	Serum Phosphate	Serum Calcium	Serum ALP	Other Features
Vitamin D deficiency	Decreased	Decreased to normal	Increased	Decreased calcitriol
Hypophosphatemia	Decreased	Normal	Decreased to normal	
Proximal RTA	Decreased	Normal	Normal	Associated with hyperchloremic metabolic acidosis
Conditions associated with abnormal matrix formation	Normal	Normal	Normal	

- radiologic findings
  - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profundus hip deformity
- bone biopsy: usually not necessary but considered the gold standard for diagnosis

### Treatment

- definitive treatment depends on the underlying cause
- vitamin D supplementation
- $\text{PO}_4^{3-}$  supplements if low serum  $\text{PO}_4^{3-}$ ,  $\text{Ca}^{2+}$  supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis

## Renal Osteodystrophy

- changes to mineral metabolism and bone structure secondary to chronic kidney disease
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoid
- metastatic calcification secondary to hyperphosphatemia may occur

### Pathophysiology

- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)<sub>2</sub>-Vit. D synthesis) and loss of renal mass (reduced 1- $\alpha$ -hydroxylase)

### Clinical Features

- soft tissue calcifications → necrotic skin lesions if vessels involved
- osteodystrophy → generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

### Investigations

- serum Ca<sup>2+</sup> corrected for albumin, PO<sub>4</sub><sup>3-</sup>, PTH, ALP,  $\pm$  imaging (x-ray, BMD),  $\pm$  bone biopsy

### Treatment

- prevention
  - maintenance of normal serum Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> by restricting PO<sub>4</sub><sup>3-</sup> intake to 1 g OD
  - Ca<sup>2+</sup> supplements; PO<sub>4</sub><sup>3-</sup> binding agents (calcium carbonate, aluminum hydroxide)
  - vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

## Paget's Disease of Bone

### Definition

- a metabolic disease characterized by excessive bone destruction and repair

### Epidemiology

- a common disease: 5% of the population, 10% of population >80 yr old

### Etiology and Pathophysiology

- postulated to be related to a slow progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

### Differential Diagnosis

- primary bone lesions
  - osteogenic sarcoma
  - multiple myeloma
  - fibrous dysplasia
- secondary bone lesions
  - osteitis fibrosa cystica
  - metastases

### Clinical Features

- usually asymptomatic (routine x-ray finding or elevated ALP)
- severe bone pain (e.g. pelvis, femur, tibia) is often the presenting complaint
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- skull involvement: headaches, increased hat size, deafness
- increased warmth over involved bones due to increased vascularity
- high output congestive heart failure
- hypercalcemia with immobilization
- osteosarcoma



#### Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget's Disease *NEJM* 2005;353:898-908

**Study:** Two identical, randomized, double-blind, actively controlled trials (combined for analysis).  
**Patients:** 357 men and women who were older than 30 yr of age and had radiologically confirmed Paget's disease. All but 4 patients had alkaline phosphatase levels that were more than twice the upper limit of normal.

**Intervention:** One 15-min infusion of 5 mg of zoledronic acid compared with 60 d of oral risedronate (30 mg/d) with follow up at 6 mo.

**Primary Outcome:** Rate of therapeutic response at 6 mo, defined as a normalization of alkaline phosphatase levels or a reduction of at least 75% in the total alkaline phosphatase excess.

**Results:** At 6 mo, 96% of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3% of patients receiving risedronate (127 of 171,  $P < 0.001$ ). Alkaline phosphatase levels normalized in 88.6% of patients in the zoledronic acid group and 57.9% of patients in the risedronate group ( $P < 0.001$ ). Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 89 d,  $P < 0.001$ ). Quality of life increased significantly from baseline at both 3 and 6 mo in the zoledronic acid group and differed significantly from those in the risedronate group at 3 mo. Pain scores improved in both groups. During post-trial follow-up (median, 190 d), 21 of 82 patients in the risedronate group had a loss of therapeutic response, as compared with 1 of 113 patients in the zoledronic acid group ( $P < 0.001$ ).

**Conclusions:** A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget's disease than does daily treatment with risedronate.

### Investigations

- laboratory
  - ↑↑ serum ALP (unless burnt out),  $\text{Ca}^{2+}$  normal or ↑,  $\text{PO}_4^{3-}$  normal
  - urinary hydroxyproline ↑ (indicates resorption)
- imaging
  - bone scan to evaluate the extent of disease
  - skeletal survey: involved bones are denser and expanded with cortical thickening
    - initial lesion may be destructive and radiolucent
    - multiple fissure fractures in long bones

### Complications

- local
  - fractures; osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
    - indicated by marked bone pain, new lytic lesions and sudden increased ALP
- systemic
  - hypercalcemia and nephrolithiasis
  - high output congestive heart failure due to increased vascularity

### Treatment

- symptomatic therapy (pain management)
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
- treat medically if ALP >3x normal
  - bisphosphonates, e.g. alendronate 40 mg PO OD x 6 mo OR risedronate 30 mg PO OD x 3 mo OR zoledronic acid 5 mg IV per year
  - calcitonin 50-100 U/d SC
- surgery for fractures, deformity, degenerative changes

## Male Reproductive Endocrinology



### Androgen Regulation

- negative feedback may occur by androgens directly or after conversion to estrogen
- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

### Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm)
- LH, FSH, total and/or bioavailable testosterone
- human chorionic gonadotropin (hCG) stimulation test
  - assesses ability of Leydig cell to respond to gonadotropin
- semen analysis
  - semen volume, sperm count, morphology and motility
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

### Hypogonadism and Infertility

- see [Urology](#), U34
- deficiency in gametogenesis or testosterone production

### Etiology

- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure) and idiopathic
- primary hypogonadism is more common than secondary

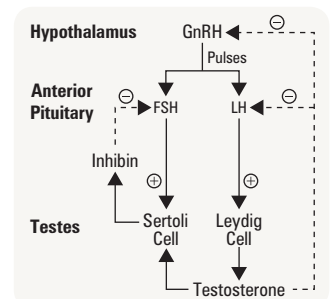


Figure 18. Hypothalmo-pituitary-gonadal axis



**Table 38. Classification and Features of Hypogonadism**

	<b>Hypergonadotropic Hypogonadism (Primary Hypogonadism)</b>	<b>Hypogonadotropic Hypogonadism (Secondary Hypogonadism)</b>
<b>Definition</b>	Primary testicular failure ↑ LH and FSH, ↑ FSH:LH ratio ↓ testosterone and sperm count	Hypothalamic-pituitary axis failure ↓ LH + FSH ↓ testosterone and sperm count
<b>Etiology</b>	Congenital: <ul style="list-style-type: none"> <li>Chromosomal defects (Klinefelter's, Noonan)</li> <li>Cryptorchidism</li> <li>Male pseudohermaphroditism</li> <li>Bilateral anorchia (vanishing testicle syndrome)</li> <li>Myotonic dystrophy</li> <li>Mutation of FSH or LH receptor gene</li> <li>Disorders of androgen synthesis</li> </ul> Germ cell defects <ul style="list-style-type: none"> <li>Sertoli cell only syndrome</li> <li>Leydig cell aplasia/failure</li> </ul> Infection/Inflammation <ul style="list-style-type: none"> <li>Orchitis – TB, lymphoma, mumps, leprosy</li> <li>Genital tract infection</li> </ul> Physical factors <ul style="list-style-type: none"> <li>Trauma, heat, irradiation, testicular torsion, varicocele</li> </ul> Drugs <ul style="list-style-type: none"> <li>Marijuana, alcohol, chemotherapy, ketoconazole, glucocorticoid, spironolactone</li> </ul> Autoimmune (antisperm antibodies)           Chronic systemic diseases (AIDS)           Idiopathic	Congenital <ul style="list-style-type: none"> <li>Kallman's syndrome</li> <li>Prader-Willi syndrome</li> <li>Abnormal subunit of LH or FSH</li> </ul> Infection <ul style="list-style-type: none"> <li>Tuberculosis, meningitis</li> </ul> Endocrine <ul style="list-style-type: none"> <li>Adrenal androgen excess</li> <li>Cushing's syndrome</li> <li>Hypo or hyperthyroidism</li> <li>Hypothalamic-pituitary disease (tumour, hyperprolactinemia, hypopituitarism)</li> </ul> Drugs <ul style="list-style-type: none"> <li>Alcohol, marijuana, spironolactone, ketoconazole, GnRH agonists, androgen/estrogen/progestin use, chronic narcotic use</li> </ul> Chronic illness <ul style="list-style-type: none"> <li>Cirrhosis, chronic renal failure, AIDS</li> <li>Sarcoidosis, Langerhan's cell histiocytosis, hemochromatosis</li> </ul> Critical illness <ul style="list-style-type: none"> <li>Surgery, MI, head trauma</li> </ul> Obesity           Idiopathic
<b>Diagnosis</b>	<b>Testicular size and consistency (soft/firm)</b> Sperm count LH, FSH, total and/or bioavailable testosterone hCG stimulation Karyotype	<b>Testicular size and consistency (soft/firm)</b> Sperm count LH, FSH, total and/or bioavailable testosterone Prolactin levels MRI of hypothalamic-pituitary region

**Treatment**

- testosterone replacement (improve libido, muscle mass, strength, hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
  - side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy
  - contraindicated if history of prostate cancer
- GnRH agonist to restore fertility, if hypothalamic dysfunction with intact pituitary
  - administered SC in pulsatile fashion using an external pump
- hCG ± human menopausal gonadotropin (hMG) (to supply FSH) can be used to restore fertility in cases of either hypothalamic or pituitary lesions
- surgery – only if testicular tissues are not functioning

**Other Causes of Male Infertility**

- hereditary disorders: Kartagener syndrome, cystic fibrosis
- anatomy: hypospadias, retrograde ejaculation
- obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- surgery: TURP, radical prostatectomy, orchiectomy

**DEFECTS IN ANDROGEN ACTION****Etiology**

- complete androgen insensitivity (testicular feminization)
- incomplete androgen insensitivity
  - 5- $\alpha$ -reductase deficiency
  - mixed gonadal dysgenesis
  - defects in testosterone synthesis
- infertile male syndrome
- undervirilized fertile male syndrome

**Clinical Features**

- depends on age of onset

**Two Distinct Features of Primary Hypogonadism**

- The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level
- Likely to be associated with gynecomastia

**Two Features of Secondary Hypogonadism**

- Associated with an equivalent decrease in sperm count and serum testosterone
- Less likely to be associated with gynecomastia

**Approach to Male Infertility**

**Infertility:** failure of a couple to conceive after 12 mo of regular intercourse without use of contraception in women <35 yr of age; and after 6 mo of regular intercourse without use of contraception in women ≥35 yr.

**History**

- Partner status re: infertility
- Length of time for attempt to conceive
- Prior successes with other partners
- Ejaculation problems
- Frequency of intercourse
- Prev Surg, Med Hx, STI Hx
- Hx orchitis? Cryptorchidism?
- Hx toxic exposure?
- Medications
- Alcohol and illicit drug use
- Heat exposure: bath, sauna, whirlpool
- Smoking

**P/E**

- General (height, weight, gynecomastia, masculine)
- Testicular size and consistency
- Varicocele?
- Pituitary disease?
- Thyroid disease?

**Investigations**

Should be considered for couples unable to conceive after 12 mo of unprotected and frequent intercourse. Consider earlier evaluation if suggestive medical hx and physical, and in women ≥35 yr of age

- Semen analysis x 2 (sperm count, morphology, motility)
- Scrotal/testicular U/S (look for varicocele)
- Bloodwork: LH, FSH, testosterone, prolactin, thyroid function tests, DNA fragmentation of sperm, karyotype, Y chromosome deletion
- Test female partner (see **Gynecology**, GY22)

**Treatment**

- No specific therapy for majority of cases
- Treat specific causes
- Consider: intrauterine insemination, IVF, therapeutic donor insemination, testicular aspiration of sperm, adoption



**Table 39. Effects of Testosterone Deficiency**

<b>First trimester in utero</b>	Incomplete virilization of external genitalia (ambiguous genitalia) Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphroditism)
<b>Third trimester in utero</b>	Micropenis Cryptorchidism (failure of normal testicular descent)
<b>Prepuberty</b>	Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair) Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones) Poor muscle development, reduced peak bone mass
<b>Postpuberty</b>	Decrease in energy, mood, and libido Fine wrinkles in corners of mouth and eyes Decrease in pubic/axillary hair, hematocrit, muscle mass, strength and BMD

Adapted from UpToDate, 2010 + Cecil's Essentials of Medicine

**Treatment**

- appropriate gender assignment in the newborn
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)
- reduction mammoplasty for gynecomastia

**Erectile Dysfunction**

- see [Urology](#), U30

**Gynecomastia****Definition**

- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals and does not warrant further evaluation

**Etiology****Physiologic**

- puberty
- elderly (involutional)
- neonatal (maternal hormone)

**Pathologic**

- endocrinopathies: primary or secondary hypogonadism, hyperthyroidism, extreme hyperprolactinemia, adrenal disease
- tumours: pituitary, adrenal, testicular, breast, ectopic production of hCG
- chronic diseases: cirrhosis, renal, malnutrition (with refeeding)
- drugs: estrogens and estrogen agonists, spironolactone, ketoconazole, cimetidine, digoxin, chemotherapy, marijuana, alcohol
- congenital/genetic: Klinefelter's syndrome, androgen insensitivity
- other: idiopathic, familial

**Pathophysiology**

- decreased androgen production + increased estrogen production
- increased availability of estrogen precursors for peripheral conversion to estrogen
- androgen receptor blockage + binding of androgen to sex hormone binding globulin (SHBG)

**History**

- recent change in breast characteristics
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction

**Occurrence of Gynecomastia**

3 peaks	% affected
Infancy	60-90
Puberty	4-69
Ages 50-80	24-65

**Causes of Gynecomastia****DOC TECH**

Drugs  
Other  
Congenital  
Tumour  
Endocrine  
CHronic disease

**Physical Exam**

- signs of feminization
- breast
  - must differentiate from breast cancer (unilateral, eccentric, hard/firm mass, fixed to underlying tissue) with possible skin changes (dimpling, retraction) or nipple changes (discharge, crusting)
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue, and no discrete mass is palpable
- genito-urinary exam
- stigmata of liver or thyroid disease

**Investigations**

- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated need to locate the primary tumour)
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
- testicular U/S to rule out testicular mass
- MRI of hypothalamic-pituitary region if pituitary adenoma suspected

**Treatment**

- initial observation for most men with gynecomastia
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen, clomiphene
- surgical
  - usually required for macromastia; gynecomastia present for >1 yr (fibrosis is unresponsive to medication); or failed medical treatment and for cosmetic purposes

## Female Reproductive Endocrinology

- see [Gynecology](#), GY4



## Paraneoplastic Syndrome

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

**Table 40. Clinical Presentation**

Syndrome Class	Symptoms/Syndrome	Associated Malignancies	Mechanism
<b>Endocrine</b>	Cushing's syndrome	Small-cell lung cancer Pancreatic carcinoma Neural tumours Thymoma	Ectopic ACTH and ACTH-like substance secretion
	SIADH	Small-cell lung cancer CNS malignancies	Antidiuretic hormone secretion
	Hypercalcemia	Lung cancer Breast carcinoma Renal cell carcinoma Multiple myeloma Ovarian carcinoma	PTH-related protein, TGF- $\alpha$ , TNF secretion
	Hypoglycemia	Hepatocellular carcinoma Fibrosarcoma	Insulin or insulin-like substance secretion
	Carcinoid	Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin secretion
<b>Neurologic</b>	Lambert-Eaton myasthenic syndrome (LEMS) • muscle weakness in limbs	Small-cell lung cancer	Ab interferes with ACh release
	Myasthenia gravis • fluctuating muscle weakness and fatiguability	Thymoma	Ab interferes with ACh release
	Paraneoplastic limbic encephalitis • depression, seizures, short-term memory loss	Small-cell lung cancer	Unknown
<b>Renal</b>	Hypokalemic nephropathy	Small-cell lung cancer	Ectopic ACTH and ACTH-like substance secretion
	Nephrotic syndrome	Lymphoma Melanomas	Immunocomplex sedimentation in nephrons
<b>GI</b>	Watery diarrhea	Medullary thyroid carcinomas	Prostaglandin secretion
<b>Hematologic</b>	Erythrocytosis	Renal cell carcinoma Hepatocellular carcinoma	EPO production
<b>Rheumatologic</b>	SLE	Lymphomas Lung cancer Breast carcinoma Gonadal carcinoma	Anti-nuclear Ab production
	Scleroderma	Breast carcinoma Lung cancer Uterine cancer	Anti-nuclear Ab production

### Investigations

- CBC, electrolytes, creatinine, LFTs, ALP, ESR, C-reactive protein, serum/urine electrophoresis,
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, PET scan
- $\pm$  endoscopy

### Treatment

- treat underlying tumour: surgery, radiation, chemotherapy
- treat immune-mediated disorder: IVIG, steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)

## Common Medications

## Diabetes Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects	Comments
Biguanide	<ul style="list-style-type: none"> <li>Sensitizes peripheral tissues to insulin → increases glucose uptake</li> <li>Decreases hepatic glucose production by stimulation of hepatic AMP-activated protein kinase (AMPK)</li> </ul>	metformin	Glucophage® Glumetza®		500 mg OD titrated to 2000 mg/d maximum	<ul style="list-style-type: none"> <li>Useful in obese Type 2 DM</li> <li>Improves both fasting and postprandial hyperglycemia</li> <li>Also ↓ TG</li> </ul>	<b>ABSOLUTE:</b> <ul style="list-style-type: none"> <li>Moderate to severe liver dysfunction</li> <li>Moderate renal dysfunction GFR &lt;30 mL/min</li> <li>Cardiac dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>GI upset (abdo discomfort, bloating, diarrhea)</li> <li>Lactic acidosis</li> <li>Anorexia</li> </ul>	↓ HbA1c 1.0-2.0%
Insulin secretagogue	<ul style="list-style-type: none"> <li>Stimulates insulin release from β cells by causing K<sup>+</sup> channel closure → depolarization → Ca<sup>2+</sup> mediated insulin release</li> <li>Use in nonobese Type 2 DM</li> </ul>	sulfonylureas: glyburide	Diabeta® Euglucon®	Micronase® Glynase PreTab®	2.5-5.0 mg/d titrated to >5 mg bid Max: 20 mg/d		<b>ABSOLUTE:</b> <ul style="list-style-type: none"> <li>Moderate to severe liver dysfunction</li> </ul> <b>RELATIVE (glyburide and glimepiride):</b> <ul style="list-style-type: none"> <li>Adjust dose in mild to moderate kidney dysfunction and avoid in severe kidney dysfunction</li> <li>Avoid glyburide in the elderly</li> </ul> <b>INTERACTIONS:</b> <ul style="list-style-type: none"> <li>Do not combine with a non-sulfonylurea insulin secretagogue or preprandial insulin</li> </ul>	<ul style="list-style-type: none"> <li>Hypoglycemia</li> <li>Weight gain</li> </ul>	↓ HbA1c 1.0-2.0%
		gliazide	Diamicon® Diamicon® MR		40-160 mg bid 30-120 mg OD				
		glimepiride	Amaryl®		1-8 mg OD				
		non-sulfonylureas: repaglinide	GlucNorm®		0.5-4 mg tid	<ul style="list-style-type: none"> <li>Short t<sub>1/2</sub> of 1 h causes brief but rapid ↑ in insulin, therefore effective for post-prandial control</li> </ul>	<b>ABSOLUTE:</b> <ul style="list-style-type: none"> <li>Severe liver dysfunction</li> </ul> <b>INTERACTIONS:</b> <ul style="list-style-type: none"> <li>Do not combine with a non-sulfonylurea or pre-prandial insulin</li> </ul>	<ul style="list-style-type: none"> <li>Hypoglycemia</li> <li>Weight gain</li> </ul>	↓ HbA1c 1.0-1.5% for repaglinide and 0.5-1.0% for nateglinide
Insulin sensitizers (thiazolidinedione)	<ul style="list-style-type: none"> <li>Sensitizes peripheral tissues to insulin → increases glucose uptake</li> <li>Decreases FFA release from adipose</li> <li>Binds to nuclear receptor PPAR-γ</li> </ul>	rosiglitazone	Avandia®		2-8 mg OD	<ul style="list-style-type: none"> <li>Rosiglitazone – indicated only in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance</li> </ul>	<b>ABSOLUTE:</b> <ul style="list-style-type: none"> <li>NYHA &gt; class II CHF</li> </ul> <b>INTERACTIONS:</b> <ul style="list-style-type: none"> <li>Do not combine with insulin</li> </ul>	<ul style="list-style-type: none"> <li>Peripheral edema</li> <li>CHF</li> <li>Anemia</li> <li>Fluid retention and congestive heart failure</li> <li>Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing)</li> <li>Increased risk of bladder cancer with pioglitazone</li> <li>Fractures</li> </ul>	↓ HbA1c 1.0-1.5%
		pioglitazone	Actos®		15-45 mg OD				
α-glucosidase inhibitor	<ul style="list-style-type: none"> <li>↓ carbohydrate GI absorption by inhibiting brush border α-glucosidase</li> </ul>	acarbose	Glucobay®		25 mg OD titrated to 100 mg tid	<ul style="list-style-type: none"> <li>↓ postprandial hyperglycemia</li> </ul>	<b>ABSOLUTE:</b> <ul style="list-style-type: none"> <li>Inflammatory bowel disease</li> <li>Severe liver dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>Flatulence</li> <li>Abdominal cramps</li> <li>Diarrhea</li> </ul>	↓ HbA1c 0.5-1.0%
Dipeptidyl peptidase-IV (DPP-IV) inhibitor	<ul style="list-style-type: none"> <li>Inhibits degradation of endogenous antihyperglycemic incretin hormones</li> <li>Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emptying</li> </ul>	sitagliptin	Januvia®		100 mg OD		<b>ABSOLUTE (sitagliptin):</b> <ul style="list-style-type: none"> <li>Type 1 DM</li> <li>DKA</li> </ul>	<ul style="list-style-type: none"> <li>Nasopharyngitis</li> <li>URT</li> <li>Headache</li> <li>Pancreatitis</li> <li>Steven-Johnson syndrome</li> </ul>	↓ HbA1c 0.5-1.0%
		saxagliptin	Onglyza™		2.5-5 mg OD				
		linagliptin	Trajenta®		5 mg OD		<b>RELATIVE (sitagliptin and saxagliptin):</b> <ul style="list-style-type: none"> <li>Use with dose reduction in kidney dysfunction</li> </ul>		
Glucagon-like peptide (GLP)-1 analogue	<ul style="list-style-type: none"> <li>Binds to GLP-1 receptor to promote insulin release</li> <li>Insulinotropic effect suppressed as plasma glucose &lt;4 mmol/L</li> <li>Slows gastric emptying, suppress inappropriately elevated glucagon levels</li> <li>Causes β-cell regeneration and differentiation in vitro</li> </ul>	Exenatide		Byetta®	5-10 µg SC bid 1 h before meals		<b>ABSOLUTE:</b> <ul style="list-style-type: none"> <li>Type 1 DM</li> <li>DKA</li> <li>Acute pancreatitis hx</li> </ul> <b>RELATIVE:</b> <ul style="list-style-type: none"> <li>Gastroparesis</li> <li>ESRD</li> <li>Personal or family history of medullary thyroid cancer (MTC)</li> </ul>	<ul style="list-style-type: none"> <li>Nausea, vomiting, diarrhea</li> <li>Dizziness, headache</li> <li>Muscle weakness</li> <li>Anti-exentide antibodies</li> <li>Pancreatitis</li> </ul>	↓ HbA1c 1.0-1.5%
		Liraglutide		Victoza®	0.6-1.8 mg OD SC				

For insulin formulations, please refer to E9

## Dyslipidemia Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
HMG CoA reductase inhibitor	• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑ LDL clearance, modest ↑ HDL, limited ↓ VLDL	atorvastatin fluvastatin lovastatin pravastatin rosuvastatin simvastatin	Lipitor® Lescol® Mevacor® Pravachol® Crestor® Zocor®		10-80 mg/d 20-80 mg/d 20-80 mg/d 10-40 mg/d 5-40 mg/d 10-80 mg/d	• 1 <sup>st</sup> line monotherapy • Used for ↑ LDL, ↑ TG	• Active liver disease • Persistent ↑ in AST, ALT unexplained	• GI symptoms • Rash, pruritus • ↑ liver enzymes • Myositis (↑ risk if combined with fibrates) • Rhabdomyolysis
Fibrates	• Upregulate lipoprotein lipase + apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL	bezafibrate fenofibrate gemfibrozil	Bezalip® Lipidil® Lopid®		400 mg/d 48-200 mg/d 600-1200 mg/d	• Used for ↑ TG, hyperchylomicronemia	• Hepatic disease • Renal disease	• GI upset • Skin rashes • ↑ risk of gallstone formation • ↑ risk of rhabdomyolysis when combined with statins
Niacin	• Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL; decreased clearance of HDL	nicotinic acid	Niaspan® generic niacin	Niacor®	0.5-2 g/d 1-3 g/d	• Used for ↑ LDL, ↑ VLDL	• Hypersensitivity • Hepatic dysfunction • Active PUD • Hyperuricemia	• Generalized flushing • Abnormal liver enzymes • Pruritus • IGT • Watch glucose control with overt DM
Bile acid sequestrants	• Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL	cholestyramine  colestipol	Questran®  Colestid®		2-24 g/d  5-30 g/d	• Used for ↑ LDL • Use as adjunct with statins or fibrates	• Complete biliary obstruction • Pregnancy, lactation • TG > 3.5 mmol/L • GI motility disorder	• Constipation • Nausea • Flatulence • Bloating • Rise in TG
Cholesterol absorption inhibitors	• Inhibits cholesterol absorption at the small intestine brush border	ezetimibe	Ezetrol®	Zetia®	10 mg/d	• Used for ↑ LDL, apo B	• Hypersensitivity • Hepatic dysfunction • Don't combine with fibrates or bile acid resins	• Fatigue • Pharyngitis • Sinusitis • Abdominal pain • Diarrhea • Arthralgia

## Thyroid Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Antithyroid Agent (thionamides)	• Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T <sub>4</sub> and T <sub>3</sub> • PTU also interferes with conversion of T <sub>4</sub> to T <sub>3</sub>	propylthiouracil (PTU)  methimazole (MMI)	Propyl-Thyracil®  Tapazole®		Start 100 mg PO tid, then adjust accordingly Thyroid storm: start 200-300 PO qid, then adjust accordingly  Start 5-20 mg PO OD, then adjust accordingly Up to 60 mg OD may be required	• Hyperthyroidism	• Hypersensitivity • Relative: renal failure, liver disease • PTU recommended in 1st trimester, MMI during 2nd and 3rd trimester. • Lactation: safe with PTU <300 mg/day and MMI <20-30 mg/d	• Nausea, vomiting • Rash • Drug-induced hepatitis • Agranulocytosis • Hepatitis with PTU • Cholestasis with MMI
Thyroid hormone	• Synthetic form of thyroxine (T <sub>4</sub> )	levothyroxine l-thyroxine	Synthroid® Eltroxin®	Levoxy®	0.05-2.0 mg/d, usually 1.6 times weight in kg is dose in micrograms In elderly patients start at 0.025 mg/d	• Hypothyroidism	• Recent MI, thyrotoxicosis	• If wrong dosing: symptoms of hypothyroidism or hyperthyroidism • Skin rash from dye in pill
Antithyroid Agent Radiopharmaceutical	• Radioactive isotope of iodine that is incorporated into the thyroid gland irradiating the area and destroying local glandular tissue	sodium iodide I-131	Iodotope®		Dose corrected for 24 h radioactive iodine uptake. Hyperthyroidism 4-12 mCi Thyroid Ca 50-150 mCi	• Hyperthyroidism • Thyroid Malignancy	• Hypersensitivity • Concurrent antithyroid medication • Pregnancy, lactation	• Nausea, vomiting • Bone marrow suppression • Sialadenitis • Thyroiditis

## Metabolic Bone Disease Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Bisphosphonates	• Inhibits osteoclast-mediated bone resorption	alendronate	Fosamax®		Osteoporosis: 5-10 mg OD 70 mg once weekly Paget's: 40 mg OD for 6 mo	<ul style="list-style-type: none"> <li>Prevention of postmenopausal osteoporosis</li> <li>Treatment of osteoporosis</li> <li>Glucocorticoid-induced osteoporosis</li> <li>Paget's disease</li> </ul>	<ul style="list-style-type: none"> <li>Esophageal stricture or achalasia (oral)</li> <li>Unable to stand or sit upright for &gt;30 min (oral)</li> <li>Hypersensitivity</li> <li>Hypocalcemia</li> <li>Renal insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>GI</li> <li>MSK pain</li> <li>Headache</li> <li>Osteonecrosis of the jaw</li> </ul>
		risedronate	Actonel®		Osteoporosis: 5 mg OD 35 mg once weekly 150 mg once monthly Paget's: 30 mg OD for 2 mo	<ul style="list-style-type: none"> <li>Treatment and prevention of postmenopausal osteoporosis</li> <li>Treatment and prevention of glucocorticoid-induced osteoporosis</li> <li>Paget's disease</li> </ul>		
		etidronate	Didronel®		Paget's: 5-10 mg /kg OD x 6 mo	<ul style="list-style-type: none"> <li>Symptomatic Paget's disease</li> <li>Prevention and treatment of heterotopic ossification after total hip replacement or spinal cord injury</li> </ul>		
		ibandronate	Boniva®		2.5 mg OD or 150 mg once monthly	<ul style="list-style-type: none"> <li>Treatment and prevention of postmenopausal osteoporosis (US only)</li> </ul>		
		pamidronate	Aredia®		Hypercalcemia of malignancy 60-90 mg IV over 2-24 h Wait at least 7 d before considering retreatment	<ul style="list-style-type: none"> <li>Hypercalcemia of malignancy</li> <li>Paget's disease</li> <li>Osteolytic bone metastases of breast cancer</li> <li>Osteolytic lesions of multiple myeloma</li> </ul>		
		zoledronate	Zometa® Aclasta®		5 mg IV once yearly IV	<ul style="list-style-type: none"> <li>Treatment of osteoporosis</li> <li>Hypercalcemia of malignancy</li> <li>Treatment and prevention of skeletal complications related to cancer</li> </ul>		
Selective Estrogen Receptor Modulators	• Decreases resorption of bone through binding to estrogen receptors	raloxifene	Evista®		60 mg OD	<ul style="list-style-type: none"> <li>Treatment and prevention of postmenopausal osteoporosis (2nd line)</li> </ul>	<ul style="list-style-type: none"> <li>Lactation</li> <li>Pregnancy</li> <li>Active or past history of DVT, PE or retinal vein thrombosis</li> </ul>	<ul style="list-style-type: none"> <li>Hot flashes</li> <li>Leg cramps</li> <li>Increased risk of fatal stroke, venous thromboembolism</li> </ul>
Calcitonin	• Inhibits osteoclast-mediated bone resorption	calcitonin	Miacalcin®		One spray (200 IU) per day, alternating nostrils	<ul style="list-style-type: none"> <li>Treatment of postmenopausal osteoporosis, greater than 5 yr postmenopause</li> </ul>	<ul style="list-style-type: none"> <li>Clinical allergy to salmon-calcitonin</li> </ul>	<ul style="list-style-type: none"> <li>Rhinitis</li> <li>Epistaxis</li> <li>Sinusitis</li> <li>Nasal dryness</li> </ul>
Anti-RANKL monoclonal Ab	• Inhibits RANKL (osteoclast differentiating factor) → inhibit osteoclast formation and decrease bone resorption	denosumab	Prolia™	Xgeva™	60 mg SC q6mo	<ul style="list-style-type: none"> <li>Treatment of postmenopausal women at high risk of fracture</li> <li>Prevent skeletal-related events in patients with bone metastasis from solid tumours</li> </ul>	<ul style="list-style-type: none"> <li>Hypocalcemia</li> </ul>	<ul style="list-style-type: none"> <li>Fatigue/headache</li> <li>Dermatitis/rash</li> <li>Hypophosphatemia/Hypocalcemia</li> <li>Hypercholesterolemia</li> <li>GI discomfort</li> </ul>
PTH	• Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity	teriparatide	Forteo®		20 µg SC OD X 18-24 mo	<ul style="list-style-type: none"> <li>Treatment of postmenopausal women with osteoporosis who are at high risk for fracture</li> <li>Treatment of men with primary or hypogonadal osteoporosis who are at high risk for fracture</li> </ul>	<ul style="list-style-type: none"> <li>Paget's disease</li> <li>Prior external beam or implant radiation therapy involving the skeleton</li> <li>Bone metastases</li> <li>Metabolic bone diseases other than osteoporosis</li> </ul>	<ul style="list-style-type: none"> <li>Orthostatic hypotension</li> <li>Hypercalcemia</li> <li>Dizziness</li> <li>Leg cramps</li> </ul>



## Metabolic Bone Disease Medications (continued)

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Calcium	• Inhibits PTH secretion				1200 mg/d (including diet) Divided in 3 doses	<ul style="list-style-type: none"> <li>• Osteopenia</li> <li>• Osteoporosis</li> <li>• Prevention of metabolic bone disease</li> </ul>	<ul style="list-style-type: none"> <li>• Caution with renal stones</li> </ul>	<ul style="list-style-type: none"> <li>• Vomiting</li> <li>• Constipation</li> <li>• Dry mouth</li> </ul>
Vitamin D	• Regulation of calcium and phosphate homeostasis	cholecalciferol (vitamin D3)			800 -2000 IU/d	<ul style="list-style-type: none"> <li>• Osteopenia</li> <li>• Osteoporosis</li> <li>• Prevention of metabolic bone disease</li> </ul>	<ul style="list-style-type: none"> <li>• Caution in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia)</li> </ul>	<ul style="list-style-type: none"> <li>• Hypercalcemia</li> <li>• Headache</li> <li>• Nausea, vomiting</li> <li>• Constipation</li> </ul>
		ergocalciferol (vitamin D2)	Drisdol® Erdol®		50,000 IU/wk	<ul style="list-style-type: none"> <li>• Osteoporosis in patients with liver dysfunction, refractory rickets, hypoparathyroidism</li> </ul>	<ul style="list-style-type: none"> <li>• Hypercalcemia</li> <li>• Malabsorption syndrome</li> <li>• Decreased renal function</li> </ul>	
		calcitriol (1,25(OH) <sub>2</sub> -D)	Rocaltrol® Calcijex®		Start 0.25 µg/d Titrate up by 0.25 µg/d at 4-8 wk intervals to 0.5-1 µg/d  Start 0.25 µg/d Titrate up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d	<ul style="list-style-type: none"> <li>• Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis</li> <li>• Hypoparathyroidism</li> </ul>	<ul style="list-style-type: none"> <li>• Hypercalcemia</li> <li>• Vitamin D toxicity</li> </ul>	

## Adrenal Medications

Drug Class	Mineralocorticoid Activity	Generic Drug Name	Potency (relative to Cortisol)	Equivalent Dose (mg)	Duration of Action (t <sub>1/2</sub> in h)	Dosing	Comments
Hydrocortisone	Yes	Cortef Solu-Cortef	1.0	20	8	<u>Adrenal Crisis:</u> 50-100 mg IV bolus, then 50-100 mg q8h (continuous infusion x 24-48 h) PO once stable (50 mg q8h x 48 h, then taper over 14 d) <u>Chronic AI:</u> 15-20 mg PO OD (2/3 AM, 1/3 PM)	<ul style="list-style-type: none"> <li>• In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low K<sup>+</sup> metabolic alkalosis)</li> </ul>
Cortisone acetate	Yes	Cortisone Acetate	0.8	25	oral = 8 IM = 18+	<u>Adrenal Crisis:</u> 75-300 mg/d PO/IM divided q12-24h <u>Chronic AI:</u> 25 mg/d	<ul style="list-style-type: none"> <li>• Pro-drug which is converted to active form as hydrocortisone</li> <li>• High doses can result in mineralocorticoid side effects (see above)</li> </ul>
Prednisone	No	Prednisone	4	5	16-36	<u>Adrenal Crisis:</u> 15-60 mg/d PO qd or divided bid/qid <u>Chronic AI:</u> 5 mg daily	<ul style="list-style-type: none"> <li>• Pro-drug which is converted to active form as prednisolone</li> </ul>
Dexamethasone	No	Dexamethasone	30	0.7	36-54	<u>Adrenal Crisis:</u> 4 mg IV; repeat q2-6h if necessary	<ul style="list-style-type: none"> <li>• Used for undiagnosed adrenal insufficiency (won't interfere with measurement of serum cortisol levels)</li> </ul>

## Landmark Endocrinology Trials

Trial	Reference	Results
<b>DIABETES</b>		
ACCORD	<i>NEJM</i> 2008; 358:2560-72	Compared with standard therapy the use of intensive therapy to target normal HbA1c levels (<6%) for 3.5 yr increased mortality and did not significantly reduce major cardiovascular events
ADVANCE	<i>NEJM</i> 2008; 358:2545-59	Intensive glucose control that lowered the HbA1c value to 6.5% reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events or death from any cause. Hypoglycemia was more common in the intensive control group
BARI-2D	<i>NEJM</i> 2009; 360:2503-15	In patients with both Type 2 DM and coronary artery disease no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin
DCCT	<i>NEJM</i> 1993; 329:977-86	Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy and neuropathy) in Type 1 DM
EDIC	<i>NEJM</i> 2005; 353:2644-53	Compared with conventional therapy intensive diabetes therapy early on without macrovascular disease (goal HbA1c <6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with Type 1 DM
NAVIGATOR	<i>NEJM</i> 2010; 362:1463-90	In patients with impaired glucose tolerance, nateglinide did not reduce progression to diabetes or risk of cardiovascular events while valsartan only reduced progression to diabetes
Steno-2	<i>NEJM</i> 2008; 358:580-91	In at-risk patients with Type 2 DM intensive intervention with multiple drug combinations and behaviour modification had sustained significant beneficial effects with respect to vascular complications and mortality. Multifactorial intervention is critical in the management of Type 2 DM
UKPDS	<i>Lancet</i> 1998; 352:837-53	Intensive blood glucose control reduces microvascular but not macrovascular complications in Type 2 DM
UKPDS extension	<i>NEJM</i> 2008; 359:1577-89	Continued risk reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause 10 yr post UKPDS trial follow up in Type 2 DM
VADT	<i>NEJM</i> 2009; 360:1-11	In patients with longstanding poorly controlled Type 2 DM intensive glucose control had no significant effect on the rates of major cardiovascular events, death or microvascular complications. Adverse events, predominantly hypoglycemia, were more common in the intensive control group
<b>LIPIDS</b>		
4S	<i>Lancet</i> 1994; 344:1383-89	In patients with angina or previous MI and high total cholesterol simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty
FIELD	<i>Lancet</i> 2005; 366:1849-61	In patients with Type 2 DM not previously on statin therapy fenofibrate did not significantly reduce the risk of the primary outcome of coronary events. It did reduce non-fatal myocardial infarctions and revascularizations
HPS	<i>Lancet</i> 2002; 360:7-22	In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths and major vascular events
Jupiter	<i>NEJM</i> 2008; 359:2195-207	Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity C-reactive protein levels and no hyperlipidemia
TNT	<i>NEJM</i> 2005; 352:1425-35	Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d

## References

- Agus AZ. Etiology of hypercalcemia (internet). UpToDate; 2010 (Version 10.2). Available from: <http://www.uptodate.com>.
- Agus AZ. Overview of metabolic bone disease (internet). UpToDate; 2002 (Version 10.2). Available from: <http://www.uptodate.com>.
- American Diabetes Association. Management of dyslipidemia in adults with diabetes (position statement). *Diabetes Care* 2002;25:S74-77.
- Anderson TJ, Gregoire J, Hegele RA, Couture P, et al. 2012 Update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol* 2012;29:151-167.
- Arnold A. Classification and pathogenesis of the multiple endocrine neoplasia syndromes (internet). UpToDate; 2002 (Version 10.2). Available from: <http://www.uptodate.com>.
- Braunwald E, Fauci AS, Kasper DL, Hauser SL, et al. *Harrison's principles of internal medicine*, vol 2. New York: McGraw Hill, 2001. Chapter: Diabetes mellitus; p2109-2135.
- Burman KD. Overview of thyroiditis (internet). UpToDate; 2002 (Version 10.2). Available from: <http://www.uptodate.com>.
- Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2013;37(S1):S1-S212.
- Canadian Task Force on Preventive Health Care. Prevention of osteoporosis and osteoporotic fractures in post-menopausal women. *CMAJ* 2004;170:1665-1667.
- Cheng A, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. *CMAJ* 2005;172:213-226.
- Dayan CM. Interpretation of thyroid function tests. *Lancet* 2001;357:619-624.
- Fodor JG, Frohlich JJ, Genest JGG, McPherson PR. Recommendations for the management and treatment of dyslipidemia. *CMAJ* 2000;162:1441-1447.
- Genest J, Frohlich JJ, Fodor JG, McPherson PR. Recommendations of the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. *CMAJ* 2003;169:01-010.
- Greenspan FS, Garber DG. *Basic and clinical endocrinology*. New York: Lange Medical Books/ McGraw Hill, 2001. p100-163, 201-272, 623-761.
- Hemmingsen SS, Lund C. Gluud targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane DB Syst Rev* 6 2011;CD008143.
- Hirsch IB, Patau DS, Brunzell J. Inpatient management of adults with diabetes. *Diabetes Care* 1995;18:870-878.
- Kitabachi AE, Umpierrez GE, Murphy MB, Barret EJ, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care* 2001;24:131-152.
- Kronenberg HM, Larsen PR, Melmed S, Polonsky K. *Williams Textbook of endocrinology*, 9th ed. Philadelphia: WB Saunders, 1998.
- NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA* 2001;285:785-795.
- Orth DN. Evaluation of the response to ACTH in adrenal insufficiency (internet). UpToDate; 2002 (Version 10.2). Available from: <http://www.uptodate.com>.
- Dawson-Hughes B, Gold DT, Rodbard HW, Bonner Jr FJ, et al. *Physician's guide to prevention and treatment of osteoporosis*. Washington: National Osteoporosis Foundation, 2003.
- Rosen HN, Rosenblatt M. Overview of the management of osteoporosis in women (internet). UpToDate; 2002 (Version 10.2). Available from: <http://www.uptodate.com>.
- Ross DS. Disorders that cause hypothyroidism (internet). UpToDate; 2002 (Version 10.2). Available from: <http://www.uptodate.com>.
- Ryan EA. Pregnancy in diabetes. *Med Clin of N Amer* 1998;82:823-845.
- Collins R, Armitage J, Parish S, Sleight PR. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360:7-22.
- The Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-1389.
- Tsui E, Bamie A, Ross S, Parkes R, et al. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care* 2001;24:1722-1727.
- United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998;352:837-853.
- Young WF, Kaplan NM. Diagnosis and treatment of pheochromocytoma in adults (internet). UpToDate; 2002 (Version 10.2). Available from: <http://www.uptodate.com>.

Aaron McGregor, Joel Moktar, Amanda Ramdyal and Amirthini Tharmalingam, chapter editors  
 Maria Jogova and Howard Meng, associate editors  
 Melini Gupta, EBM editor  
 Dr. Ruby Alvi, Dr. Azadeh Moaveni and Dr. Melissa Nutik, staff editors

<b>Four Principles of Family Medicine</b> . . . . .	<b>2</b>	Domestic Violence/Elder Abuse . . . . .	<b>28</b>
<b>Periodic Health Examination (PHE)</b> . . . . .	<b>2</b>	Dyspepsia . . . . .	<b>29</b>
Purpose of the PHE		Dyspnea . . . . .	<b>29</b>
Breast Cancer Screening Guidelines		Dysuria . . . . .	<b>30</b>
Colorectal Cancer Screening Guidelines		Epistaxis . . . . .	<b>31</b>
Cervical Cancer Screening		Erectile Dysfunction (ED) . . . . .	<b>31</b>
<b>Health Promotion and Counselling</b>		Eye Complaints . . . . .	<b>32</b>
Motivational Strategies for Behavioural		Falls in the Elderly . . . . .	<b>32</b>
Change . . . . .	<b>5</b>	Fatigue . . . . .	<b>32</b>
Nutrition . . . . .	<b>5</b>	Fever . . . . .	<b>34</b>
Obesity . . . . .	<b>7</b>	Joint Pain . . . . .	<b>35</b>
Dyslipidemia . . . . .	<b>8</b>	Headache . . . . .	<b>36</b>
Exercise . . . . .	<b>10</b>	Hearing Impairment . . . . .	<b>37</b>
Smoking Cessation . . . . .	<b>10</b>	Hypertension . . . . .	<b>37</b>
Alcohol . . . . .	<b>12</b>	Low Back Pain . . . . .	<b>41</b>
<b>Common Presenting Problems</b>		Menopause/Hormone Replacement Therapy (HRT) . . . . .	<b>42</b>
Abdominal Pain . . . . .	<b>13</b>	Osteoarthritis . . . . .	<b>43</b>
Allergic Rhinitis . . . . .	<b>13</b>	Osteoporosis . . . . .	<b>43</b>
Amenorrhea . . . . .	<b>14</b>	Rash . . . . .	<b>45</b>
Anxiety . . . . .	<b>15</b>	Rhinorrhea . . . . .	<b>46</b>
Asthma/COPD . . . . .	<b>16</b>	Sexually Transmitted Infections (STIs) . . . . .	<b>46</b>
Benign Prostatic Hyperplasia (BPH) . . . . .	<b>17</b>	Sinusitis . . . . .	<b>47</b>
Bronchitis (Acute) . . . . .	<b>18</b>	Sleep Disorders . . . . .	<b>48</b>
Chest Pain . . . . .	<b>18</b>	Sore Throat (Pharyngitis) . . . . .	<b>50</b>
Common Cold (Acute Rhinitis) . . . . .	<b>19</b>	<b>Complementary and Alternative Medicine (CAM)</b> . . . . .	<b>52</b>
Contraception . . . . .	<b>20</b>	<b>Primary Care Models</b> . . . . .	<b>53</b>
Cough . . . . .	<b>21</b>	<b>Antimicrobial Quick Reference</b> . . . . .	<b>53</b>
Dementia . . . . .	<b>21</b>	<b>References</b> . . . . .	<b>56</b>
Depression . . . . .	<b>21</b>		
Diabetes Mellitus (DM) . . . . .	<b>22</b>		
Diarrhea . . . . .	<b>26</b>		
Dizziness . . . . .	<b>26</b>		

## Acronyms

AAA	abdominal aortic aneurysm	GAD	generalized anxiety disorder	MMSE	mini mental status examination	PUD	peptic ulcer disease
ACR	albumin:creatinine ratio	GERD	gastroesophageal reflux disease	MOCA	Montreal cognitive assessment	PVD	peripheral vascular disease
AIN	anal intraepithelial neoplasia	GMC	general medical condition	MSM	men who sleep with men	RA	rheumatoid arthritis
BMI	body mass index	gtt	drops	N/V	nausea/vomiting	RCT	randomized controlled trial
ABG	arterial blood gas	HAART	highly active antiretroviral therapy	NPH	insulin human isophane	SAH	subarachnoid hemorrhage
AR	absolute reduction	HDL-C	high density lipoprotein cholesterol	NTD	neural tube defects	SDRI	serotonin dopamine reuptake inhibitor
BPPV	benign paroxysmal positional vertigo	HSIL	high-grade squamous intraepithelial lesion	NTG	nitroglycerin	SERM	selective estrogen receptor modulator
CA	cancer	HPV	human papillomavirus	O&P	ova and parasites	SIDS	sudden infant death syndrome
CABG	coronary artery bypass graft	IBD	inflammatory bowel disease	OA	osteoarthritis	SLE	systemic lupus erythematosus
CAD	coronary artery disease	IBS	irritable bowel syndrome	OCD	obsessive compulsive disorder	SNRI	serotonin norepinephrine reuptake inhibitor
CBT	cognitive behavioural therapy	ICS	inhaled corticosteroids	OCP	oral contraceptive pill	SOB	shortness of breath
CF	cystic fibrosis	IFG	impaired fasting glucose	OCPD	obsessive compulsive personality disorder	SSRI	selective serotonin reuptake inhibitor
CHF	congestive heart failure	IGT	impaired glucose tolerance	OD	once a day	TIA	transient ischemic attack
CPAP	continuous positive airway pressure	IHD	ischemic heart disease	OGCT	oral glucose challenge test	TC	total cholesterol
CRC	colorectal cancer	INH	isoniazid	OGTT	oral glucose tolerance test	TCA	tricyclic antidepressant
DHP	dihydropyridine	IIVP	intravenous pyelogram	OTC	over the counter	TG	triglyceride
DMPA	depot medroxyprogesterone	KUB	kidneys, ureter, bladder x-ray	PCOS	polycystic ovarian syndrome	TM	tympanic membrane
DRE	digital rectal exam	LDL-C	low density lipoprotein cholesterol	PFT	pulmonary function test	TMJ	temporomandibular joint
DS	double strength	LSIL	low-grade squamous intraepithelial lesion	PID	pelvic inflammatory disease	UC	ulcerative colitis
ER	emergency room	LV	left ventricle	PMS	premenstrual syndrome	URT	upper respiratory tract infection
ER	extended release	LVH	left ventricle hypertrophy	PND	paroxysmal nocturnal dyspnea	UTI	urinary tract infection
F/U	follow-up	MDI	metered dose inhaler	PPI	proton pump inhibitor	VAIN	vaginal intraepithelial neoplasia
FBG	fasting blood glucose	MAOI	monoamine oxidase inhibitor	PPD	purified protein derivative	VIN	vulvar intraepithelial neoplasia
FOBT	fecal occult blood test			PTSD	post-traumatic stress disorder	VBI	vertebrobasilar insufficiency
FRS	Framingham Risk Score					WSIB	Workplace Safety and Insurance Board

# Four Principles of Family Medicine

## College of Family Physicians of Canada Guidelines

### 1. The family physician is a skilled clinician

- in diagnosing and managing diseases common to the population served
- recognizes importance of early diagnosis of serious life-threatening illnesses

### 2. Family medicine is a community-based discipline

- provides information and access to community services
- responds/adapts to changing needs and circumstances of the community

### 3. The family physician is a resource to a defined practice population

- serves as a health resource
- advocates for public policy to promote health

### 4. The patient-physician relationship is central to the role of the family physician

- committed to the person, not just the disease
- promotes continuity of patient care



#### Patient-Centred Clinical Method

- Explore/define patient problems and decide on management together
- Consider both agendas and find common ground



#### Agendas in Family Medicine

##### Doctor's Agenda

History, physical, investigations, diagnosis, plan

##### Patient's Agenda

##### FIFE

**Feelings:** related to the illness, fears (how do you feel about what is happening?)

**Ideas:** and explanations of the cause (what do you think is going on?)

**Function:** the illness' impact on daily life (how is it affecting your work or life?)

**Expectations:** of the doctor and the illness (what were you expecting at the visit?)



#### Adult Periodic Health Exam

Male and female evidence-based preventative care checklist forms are available online at <http://www.cfpc.ca>.



#### When Ordering Fasting Bloodwork

- Routinely ordered as  $\geq 12$  h of fasting
- Remember, "fasting" means no food, no drinks (except small quantities of water), no gum, no smoking
- Prescription medications are okay unless otherwise specified
- Special care should be taken when ordering fasting bloodwork in elderly or other medically fragile patients



#### A Note About PSA:

- Routine PSA screening is currently not recommended
- PSA testing is used in ongoing surveillance and management of men with prostate cancer (see [Urology](#), U25)



#### Classification of Recommendations

- A Good** evidence to recommend the clinical preventative action.
- B Fair** evidence to recommend the clinical preventative action.
- C** Existing evidence is **conflicting** and no recommendation is made for or against use of the clinical preventative action; however, other factors may influence decision-making.
- D Fair** evidence to recommend **against** the clinical preventative action.
- E Good** evidence to recommend **against** the clinical preventative action.
- I Insufficient** evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making.

# Periodic Health Examination (PHE)

- Canadian Task Force on Preventive Health Care established in 1976, first published in 1979, last updated in 2005
- mandate: to develop and disseminate clinical practice guidelines for primary and preventive care
- recommendations are based on systematic analysis of scientific evidence
  - most notable recommendation is the abolition of the annual physical exam; replaced by the PHE

## Purpose of the PHE

- **primary prevention:** identify risk factors for common diseases; counsel patients to promote healthy behaviour
- **secondary prevention:** presymptomatic detection of disease to allow early treatment and to prevent disease progression
- update clinical data
- enhance patient-physician relationship

Table 1. Periodic Health Exam

General Population	Special Population
<b>DISCUSSION</b> <ul style="list-style-type: none"> <li>• Dental hygiene (community fluoridation, brushing, flossing) (A)</li> <li>• Noise control and hearing protection (A)</li> <li>• Screen for poverty</li> <li>• Smokers: counsel on smoking cessation, provide:               <ul style="list-style-type: none"> <li>• Nicotine replacement therapy (A)</li> <li>• Referral to smoking cessation program (B)</li> </ul> </li> <li>• Dietary advice on leafy green vegetables and fruits (B)</li> <li>• Seat belt use (B)</li> <li>• Injury prevention (bicycle helmets, smoke detectors) (B)</li> <li>• Moderate physical activity (B)</li> <li>• Avoid sun exposure and wear protective clothing (B)</li> <li>• Problem drinking screening and counselling (B)</li> <li>• Counselling to protect against STIs (B)</li> <li>• Nutritional counselling and dietary advice on fat and cholesterol (B)</li> <li>• Dietary advice on calcium and vitamin D requirements (see <a href="http://www.canadiantaskforce.ca">www.canadiantaskforce.ca</a> – for up to date guideline)</li> </ul>	<b>Pediatrics:</b> Home visits for high risk families (A) Inquiry into developmental milestones (B)  <b>Adolescents:</b> Counsel on sexual activity and contraceptive methods (B) Counsel to prevent smoking initiation (B)  <b>Perimenopausal women:</b> Adults >50: Assess for risk factors for osteoporosis and fracture (A) Counsel on osteoporosis Counsel on risks/benefits of hormone replacement therapy (B) (see <a href="http://www.canadiantaskforce.ca">www.canadiantaskforce.ca</a> – for up to date guideline)  <b>Adults &gt;65:</b> Follow-up on caregiver concern of cognitive impairment (A) Multidisciplinary post-fall assessment (A)
<b>PHYSICAL</b> <ul style="list-style-type: none"> <li>• Blood pressure measurement (B)</li> <li>• BMI measurement in obese adults (B)</li> </ul>	<b>Pediatrics:</b> Repeated examinations of hips, eyes and hearing (especially in first year of life) (A) Serial height, weight and head circumference (B) Visual acuity testing after age 2 (B)  <b>Adults &gt;65:</b> Visual acuity (Snellen sight chart) (B) Hearing impairment (inquiry, whispered voice test, audioscope) (B)  <b>First degree relative with melanoma:</b> Full body skin exam (B)

Table 1. Periodic Health Exam (continued)

General Population	Special Population
<b>TESTS</b> <ul style="list-style-type: none"> <li>Multiphase screening with the Hemoccult® test (adults age 50-75 q1-2yr) (A). See FM4</li> <li>Sigmoidoscopy (adults &gt;50) (frequency not established) (B). See FM4</li> <li>Bone mineral density: age ≤64 if at risk (see FM44 for risk factors), otherwise age ≥65</li> <li>Fasting lipid profile (C): <ul style="list-style-type: none"> <li>Women age &gt;50 or post-menopausal; earlier if at risk</li> <li>Men age &gt;40; earlier if at risk</li> <li>optimal frequency unknown, at least q5yr</li> </ul> </li> <li>Fasting blood glucose: age &gt;40 q3yr (or sooner and more frequently if risk factors present)</li> <li><b>Men:</b> <ul style="list-style-type: none"> <li>Prostate cancer screening with PSA and DRE (A) <ul style="list-style-type: none"> <li>For men &gt;50 with at least 10-yr life expectancy q2-4yr</li> <li>If family history of prostate CA or African descent screen at age 40</li> <li>See <a href="#">Urology</a>, U25</li> </ul> </li> </ul> </li> <li><b>Women:</b> <ul style="list-style-type: none"> <li>Mammography (women age 50-74) q2-3yr</li> <li>Pap smear q3yr if normal cytology (initiate at 21 yr of age for women who are or have ever been sexually active); stop at age 70 after ≥3 negative tests in 10 yr prior (2012 Ontario guidelines). See FM4</li> </ul> </li> </ul>	<b>Pediatrics:</b> <ul style="list-style-type: none"> <li>Routine hemoglobin for high risk infants (B)</li> <li>Blood lead screening of high risk infants (B)</li> </ul> <b>Diabetics:</b> <ul style="list-style-type: none"> <li>Urine dipstick (A)</li> <li>Fundoscopy (B)</li> </ul> <b>TB high risk groups:</b> Mantoux skin testing (A) <b>STI high risk groups:</b> Voluntary HIV antibody screening (A) <ul style="list-style-type: none"> <li>Gonorrhea screening (A)</li> <li>Chlamydia screening in women (B)</li> <li>Syphilis screen (A)</li> </ul> <b>Colon cancer high risk groups:</b> Colonoscopy (A) <b>FAP:</b> <ul style="list-style-type: none"> <li>Genetic testing and sigmoidoscopy annually, begin at age 10-12 (B)</li> </ul> <b>HNPCC:</b> <ul style="list-style-type: none"> <li>Colonoscopy q1-2yr, begin at age 20 or 10 yr younger than earliest case in the family (B)</li> </ul> <b>Syphilis risk group:</b> VDRL test (A)
<b>THERAPY</b> <ul style="list-style-type: none"> <li>Folic acid supplementation to women of child-bearing age (A)</li> <li>Pharmacologic treatment of hypertension with dBp &gt;90 mmHg (adults age 21-64, elderly specific subgroups) (A)</li> <li>Varicella vaccine for children age 1-12 and susceptible adolescents/adults (A)</li> <li>Rubella vaccine for all non-pregnant women of child-bearing age unless there is proof of immunity via immunization records or serology (B)</li> <li>Tetanus vaccine: routine booster q10yr if had 1° series (A)</li> <li>Pertussis vaccine: adults &lt;65 should receive one booster given as Tdap-Adacel® or Boostrix® (A)</li> <li>Herpes zoster vaccine for adults ≥60</li> </ul>	<b>Pediatrics:</b> <ul style="list-style-type: none"> <li>Routine immunizations (A)</li> <li>Hepatitis B immunization (A)</li> <li>See <a href="#">Pediatrics</a>, P3</li> </ul> <b>Females 9-45:</b> <ul style="list-style-type: none"> <li>HPV Quadrivalent Vaccine for females age 9-13, catch up age 14-45 (A)</li> </ul> <b>Influenza high risk groups:</b> Outreach strategies for vaccination (A), annual immunization (B), now recommended for all <b>TB high risk groups:</b> INH prophylaxis for household contacts or skin test converters (B) <ul style="list-style-type: none"> <li>INH prophylaxis for high risk sub-groups (B)</li> </ul> <b>Immunocompromised/age ≥65/COPD:</b> Pneumococcal vaccine (A) (Pneumovax®)

Classification of recommendation in brackets. See sidebar on FM3.

Reference: Canadian Task Force on Preventative Health Care, 2005

**Efficacy of Human Papillomavirus Vaccines – A Systematic Quantitative Review**

*Int J Gynecol Cancer* 2009;19:1166-1176  
**Study:** Systematic review of 6 randomized placebo-controlled double-blind trials.

**Patients:** 47,236 women between ages 9-26.  
**Intervention:** Vaccination with HPV L1 virus-like particle in either quadrivalent (HPV 6, 11, 16, 18), bivalent (HPV 16, 18), or univalent (HPV 16) form vs. placebo.

**Main Outcome:** Prevention of cytologically and/or histologically proven lesions (including LSIL, HSIL, VIN, VAIN, AIN, adenocarcinoma in situ of the cervix, or cancer of the cervix associated with HPV infection).

**Results:** Bivalent and quadrivalent vaccines reduced the rate of lesions in the cervix, vulva, vagina, and anogenital region with efficacy of 93% and 62%, respectively.

**Prostate-Cancer Mortality at 11 Years of Follow-up**

*NEJM* 2012;366:981-990

**Study:** Updated "ERSPC" study – multicentre randomized trial of screening for prostate cancer using PSA.

**Patients:** 162,388 men, ages 55-69 from 8 different European countries.

**Intervention:** PSA-based screening.

**Main Outcome:** mortality from prostate cancer.

**Results:** After median follow up of 11 yr, the RRR of death from prostate cancer was 21%. The ARR was 1.07 deaths/1000 men. NNT=1055 – therefore to prevent one death from prostate cancer at 11 yr follow up, 1055 men would need to be screened.

**Folic Acid Supplementation in Pregnancy (Joint SOGC-Motherisk clinical guideline)**

- To prevent neural tube defects in all women capable of becoming pregnant
- Low risk women (no personal health risks, planned pregnancy): 0.4-1.0 mg daily folic acid supplementation for at least 2-3 mo before conception and throughout pregnancy and postpartum period

- High risk women (health risks including epilepsy, insulin dependent diabetes, BMI >35, family history of NTD, high risk ethnic group): at least 3 mo prior to conception until 10-12 wk post conception: daily supplementation with multivitamins with 5 mg folic acid
- From wk 12 post-conception until postpartum period: 0.4-1.0 mg of folic acid supplementation is sufficient
- Women with additional lifestyle issues (poor compliance with medications, no birth control, additional teratogenic substances): higher folic acid dose of 5 mg

**Appropriate Use of Screening and Diagnostic Tests to Foster High-Value, Cost-Conscious Care**

*Ann Intern Med* 2012;156:147-149  
**Suggested principles for providing high-value, cost-conscious care (see article Table 1 for specific examples):**

- Diagnostic tests should not be performed if the results will not change management.
- When the pretest probability of disease is low, the likelihood of a false-positive test result is higher than the likelihood of a true-positive result. False-positive results often lead to further testing, which may be expensive and potentially harmful (e.g. anxiety for patient, inappropriate treatment).
- The true cost of a test includes not only the cost of the test itself but also the downstream costs incurred because the test was performed. These include the costs of subsequent testing, treatment, or follow-up.

## Breast Cancer Screening Guidelines

### 2011 Recommendations on screening for breast cancer in average-risk women (The Canadian Task Force on Preventative Health Care)(Weak recommendations with low-moderate quality evidence)

- average-risk women: women age 40-74 with no personal history of breast cancer, history of breast cancer in 1st degree relatives, known mutations of the *BRCA1/BRCA2* genes or previous exposures of the chest wall to radiation

#### Mammography

- age 40-49: no routine screening
- age 50-69: routine screening q2-3yr
- age 70-74: routine screening q2-3yr

#### Magnetic Resonance Imaging (MRI)

- no routine screening with MRI scans

#### Clinical Breast Examination (CBE)

- no routine CBE alone or in conjunction with mammography to screen for breast cancer

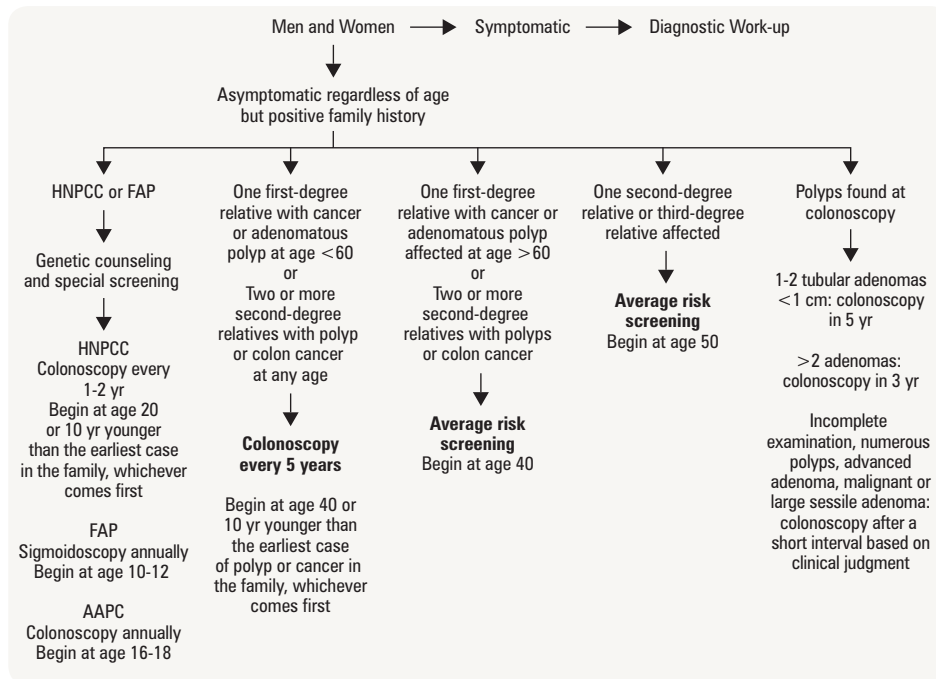
#### Breast self-examination

- recommend not advising women to routinely practice breast self-examination



## Colorectal Cancer Screening Guidelines

- recommendations for average risk individuals (asymptomatic, no history of UC, polyps, or CRC):
  - Canadian Association of Gastroenterology (2010):
    - FOBT q1-2yr
    - flexible sigmoidoscopy q10yr
    - flexible sigmoidoscopy + FOBT q5yr
    - for UC patients, colonoscopy q1-2yr after 8 yr of disease



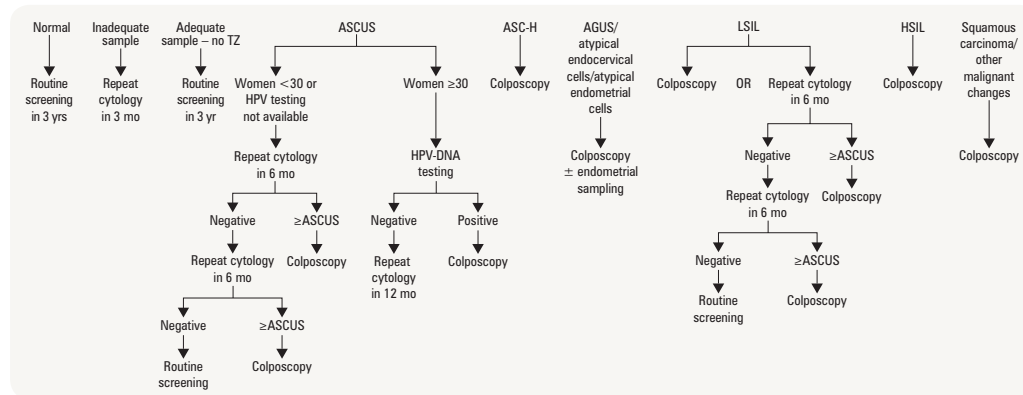
**Figure 1. Approach to higher risk screening**

AAPC = attenuated adenomatous polyposis; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; 1st degree relatives: parents, siblings, children; 2nd degree relatives: grandparents, aunts, uncles; 3rd degree relatives: great grandparents or cousins

Printed with permission from Can J Gastroenterol 2004;18:93-99

## Cervical Cancer Screening

- either conventional Papanicolaou (Pap) smear or liquid based cytology testing
- endocervical and exocervical cell sampling (aim is to sample the transitional zone)
- best identifies squamous cell abnormalities, less reliable for glandular abnormalities
  - false positives 5-10%, false negatives 10-40% (for single test)
  - false negative rate 50% for existing cervical cancer
- cervical cancer screening guidelines differ by Canadian jurisdiction (see The Society of Obstetricians and Gynaecologists of Canada updated guidelines)
- Canadian guidelines:**
  - screen all women age  $\geq 25$  q3yr
  - women age  $\geq 70$ : if 3 normal tests in a row and no abnormal tests in last 10 yr, can discontinue screening
- Ontario guidelines:**
  - screen all women age  $\geq 21$  who are or have ever been sexually active (includes intercourse or digital/oral activity with partner of either gender)
  - if cytology is normal, can screen every 3 yr
  - women age  $\geq 70$ : if 3 successive negative Pap tests in last 10 yr, can discontinue screening
- pregnant women and women who have sex with women should follow the routine cervical screening regimen
- women who have had a hysterectomy:
  - total: discontinue screening if hysterectomy was for benign disease and no history of cervical dysplasia or HPV infection
  - subtotal: continue screening according to guidelines
- exceptions to guidelines:
  - immunocompromised (transplant, steroids, diethylstilbestrol exposure, HIV)
  - adolescent women
  - previously unscreened patients



**Figure 2. Decision making chart for cervical cancer screening (not applicable for adolescents)**

TZ = transitional zone; ASCUS = abnormal squamous cells of unknown significance; LSIL = low grade squamous intraepithelial lesion; HSIL = high grade squamous intraepithelial lesion; ASC-H = abnormal squamous cells cannot rule out HSIL; AGUS = atypical glandular cells of unknown significance  
Adapted from Ontario Cervical Screening Cytology Guidelines. May 2012

## Health Promotion and Counselling

- health promotion is the most effective preventative strategy
- 40-70% of productive life lost annually is preventable
- there are several effective ways to promote healthy behavioural change, such as discussions appropriate to a patient's present stage of change

## Motivational Strategies for Behavioural Change

**Table 2. Motivational Strategies for Behavioural Change**

Patient's Stage of Change	Physician's Aim	Physician's Plan
<b>Pre-contemplation</b>	Encourage patient to consider the possibility of change Assess readiness for change Increase patient's awareness of the problem and its risks	Raise issue in a sensitive manner Offer (not impose) a neutral exchange of information to avoid resistance
<b>Contemplation</b>	Understand patient's ambivalence and encourage change Build confidence and gain commitment to change	Offer opportunity to discuss pros and cons of change using reflective listening
<b>Preparation</b>	Explore options and choose course most appropriate to patient Identify high-risk situations and develop strategies to prevent relapse Continue to strengthen confidence and commitment	Offer realistic options for change and opportunity to discuss inevitable difficulties
<b>Action</b>	Help patients design rewards for success Develop strategies to prevent relapse Support and reinforce convictions towards long-term change	Offer positive reinforcement and explore ways of coping with obstacles Encourage self-rewards to positively reinforce change
<b>Maintenance</b>	Help patient maintain motivation Review identified high-risk situations and strategies for preventing relapse	Discuss progress and signs of impending relapse
<b>Relapse</b>	Help patient view relapse as a learning experience Provide support appropriate to present level of readiness post-relapse	Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future Reassess patient's readiness to change

Adapted from Hunt P. Motivating Change. Nursing Standard 2001;16:45-52, 54-55

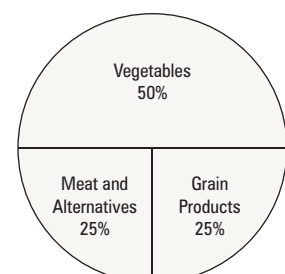
## Nutrition

### General Population

- Canada's Food Guide is appropriate for individuals age ≥2
- counsel on variety, portion size, and plate layout (see Figure 3)

**Table 3. Canada's Food Guide 2007 Recommendations for Adults**

Food Group	Servings/day	Choose More Often
Grain products	6-8	Whole grain and enriched grain products
Vegetables and fruit	7-10	Dark green vegetables, orange vegetables and fruit
Milk products	2-3 Children age 2-8: 2 Youth age 9-18: 3-4 Pregnant/breastfeeding: 3-4	Lower-fat dairy products
Meat and alternatives	2-3	Lean meat, poultry, fish, peas, beans, lentils



**Figure 3. Plate layout**

## Cardiovascular Disease Prevention

**Table 4. Dietary Guidelines for Reducing Risk of Cardiovascular Disease in General Population**

Food Item	Recommendations	Effects
<b>Fat</b>	Fat intake <30% of total energy Saturated fat <7% of total energy Trans fat <1% of total energy Cholesterol <300 mg/d	Lower LDL
<b>Omega-3 fatty acid rich foods</b>	≥2 servings/wk of fish (esp. oily fish like salmon)	Decreased sudden death, death from CAD Lower TG
<b>Salt</b>	≤2300 g/d	Lower BP
<b>Alcohol</b>	≤2 drinks/d for men ≤1 drink/d for women	Decreased risk of hypertriglyceridemia, HTN

References: Canada's Food Guide to Healthy Eating. Health Canada. Last updated 2007. <http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/>  
Lichtenstein AH, et al. Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114:82-96

**Table 5. Introduction to Vitamins and Minerals**

Vitamin/Mineral	Dietary Source	Signs of Deficiency	Signs of Toxicity
<b>Folate (vit B<sub>9</sub>)</b>	Green leafy vegetables, organ meats, dried yeast, dried beans, legumes, citrus, fortified grains	Macrocytic anemia, diarrhea, glossitis, lethargy, stomatitis <b>Very rare in Canada due to fortification of bread</b>	None known from foods, seizures
<b>Cyanocobalamin (vit B<sub>12</sub>)</b>	Organ meats, beef, pork, milk, cheese, fish	Megaloblastic anemia, glossitis, leukopenia, weakness, peripheral neuropathy (esp. foot drop)	None known from foods
<b>Ascorbic acid (vit C)</b>	Citrus fruits, tomatoes, potatoes, red berries, peppers	Scurvy, keratosis of hair follicles, impaired wound healing, anemia, depression, lethargy, bleeding	Osmotic diarrhea, N/V, oxalate kidney stones, interference with anticoagulation therapy
<b>Vitamin A</b>	Fish liver oils, egg yolk, dairy products, green leafy or orange/yellow vegetables and fruit	Dermatitis, night blindness, keratomalacia, xerophthalmia	N/V, headache, dizziness, deep bone pain, peeling skin, gingivitis, alopecia, hepatotoxicity
<b>Vitamin D</b>	Fish, fish liver oils, fortified milk, egg yolk, sunlight	Osteoporosis, osteomalacia, muscle weakness, bone pain, hypophosphatemia, hypocalcemia	Excess bone and soft tissue calcification, kidney stones, hypercalcemia, anorexia, renal failure
<b>Vitamin E</b>	Polyunsaturated vegetable oils, nuts, eggs, wheat germ, whole grains	Rare hemolysis, anemia, neuronal axonopathy, myopathy	Prolonged clotting time, impaired neutrophil function
<b>Vitamin K</b>	Green leafy vegetables, liver, vegetable oils, intestinal flora	Bleeding, purpura, bruising, prolonged clotting time	Jaundice
<b>Calcium</b>	Dairy products, dark, green and leafy vegetables, fortified soy, fortified orange juice	Tetany, arrhythmias, congestive heart failure, altered nerve conduction, osteomalacia	Metastatic calcification, weakness, renal failure, psychosis
<b>Magnesium</b>	Soy, clams, wheat germ, almonds, dairy products, green leaves, nuts, cereal grains, seafood	Weakness, convulsions, neuromuscular irritability and dysfunction, failure to thrive	Hypotension, cardiac disturbances, respiratory failure
<b>Potassium</b>	Meat, milk, bananas, prunes, raisins, oranges, grapefruits, potatoes, legumes	Polyuria, impaired muscle contraction, ECG changes (prolonged QT interval, prominent U-waves), peritoneal distention, dyspnea, paralysis, cardiac disturbances	Mental confusion, hypotension, weakness, ECG changes (flattened P-waves, wide QRS, peaked T-waves), paralysis, cardiac disturbances
<b>Iron</b>	Meat, fish, poultry, organ meats, eggs, prunes, peas, beans, lentils, soy, raisins, fortified grain products	Glossitis, fatigue, tachycardia, microcytic hypochromic anemia, koilonychia, enteropathy	Nutritional hemosiderosis, organ damage

Adapted from Mosby's Family Practice Sourcebook: An Evidence-Based Approach to Care, 4th edition, edited by Dr. Michael Evans (pp. 343-345). Copyright © 2006 Elsevier Canada, a division of Reed Elsevier Canada, Ltd. All rights reserved. Reprinted by permission of Elsevier Canada, 2009



### Handy Serving Size Comparisons

- 3 oz meat, fish, poultry → palm of hand
- 1 cup dairy (milk/yogurt) → size of fist
- Bread/grains → one slice, palm of hand
- ½ cup rice/pasta → one hand cupped
- 1 cup of fruit/vegetables → two cupped hands
- 1 oz cheese → full length of thumb
- 1 tsp oil/butter → tip of thumb
- Nuts/chips/snacks → palm covered



### Energy Content of Food

- Carbohydrates 4 kcal/g
- Protein 4 kcal/g
- Fat 9 kcal/g
- Ethanol 7 kcal/g



### Calculating Total Daily Energy Expenditure (TDEE)

- Roughly 35 kcal/kg/d
- Varies by age, weight, sex, and activity level
- Average 2000-2100 kcal/d for women, 2700-2900 kcal/d for men



### Canadian Cancer Society (CCS) Recommendations for Vitamin D Use

- Based on CCS research on Vitamin D and the prevention of colorectal, breast and prostate cancer
- In consultation with their healthcare provider, the Society is recommending that:
  - Adults living in Canada should consider taking Vitamin D supplementation of 1,000 international units (IU) a day during the fall and winter
  - Adults at higher risk of having lower Vitamin D levels should consider taking Vitamin D supplementation of 1,000 IU/d all year round. This includes people: who are older, with dark skin, who don't go outside often, and who wear clothing that covers most of their skin



### Osteoporosis Canada Recommendations for Calcium and Vitamin D Daily Requirements:

- Vitamin D: 400-800 IU for individuals age <50, 800-2000 IU for individuals age ≥50
- Calcium: 1200 mg daily from all sources for individuals age ≥50

**Table 6. Macronutrient Distribution Ranges**

Age (yr)	Macronutrient as % of Daily Calories		
	Protein	Fat	Carbohydrate
1 to 3	5-20	30-40	45-65
4 to 18	10-30	25-35	45-65
19 and older	10-35	20-35	45-65

Adapted from Dietary Reference Intakes Tables, Health Canada. [http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index\\_e.html](http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index_e.html)

**Burning Fat**

3500 kcal of energy are used for every pound of human fat burned during activity.

**Losing Weight**

- Aim for caloric intake 500-1000 kcal/d less than total daily energy expenditure (TDEE)
- Results in 1-2 lb (0.5-1 kg) weight loss per wk
- Achieved by combination of increased activity and/or decreased caloric intake

**Low BMI is associated with:**

- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications

**Adverse Medical Consequences of Obesity**

- Type 2 DM
- CAD
- Stroke
- HTN
- Gallbladder disease
- Non-alcoholic steatohepatitis
- Complications of pregnancy
- Dyslipidemia
- Osteoarthritis
- Sleep apnea
- Certain cancers
- CHF
- Low back pain
- Increased total mortality

## Obesity

- body mass index (BMI) = weight (kg)/height (m)<sup>2</sup> = weight (lbs)/height (inch)<sup>2</sup> x 703; BMI is a poor predictor of obesity
- waist circumference (WC)
  - should be measured in all adults to assess obesity-related health risks
  - specific cutoff points exist for different ethnic backgrounds (as recommended by the 2006 Canadian Clinical Practice Guidelines on obesity)
  - measurement of waist-hip ratio has no advantage over waist circumference alone

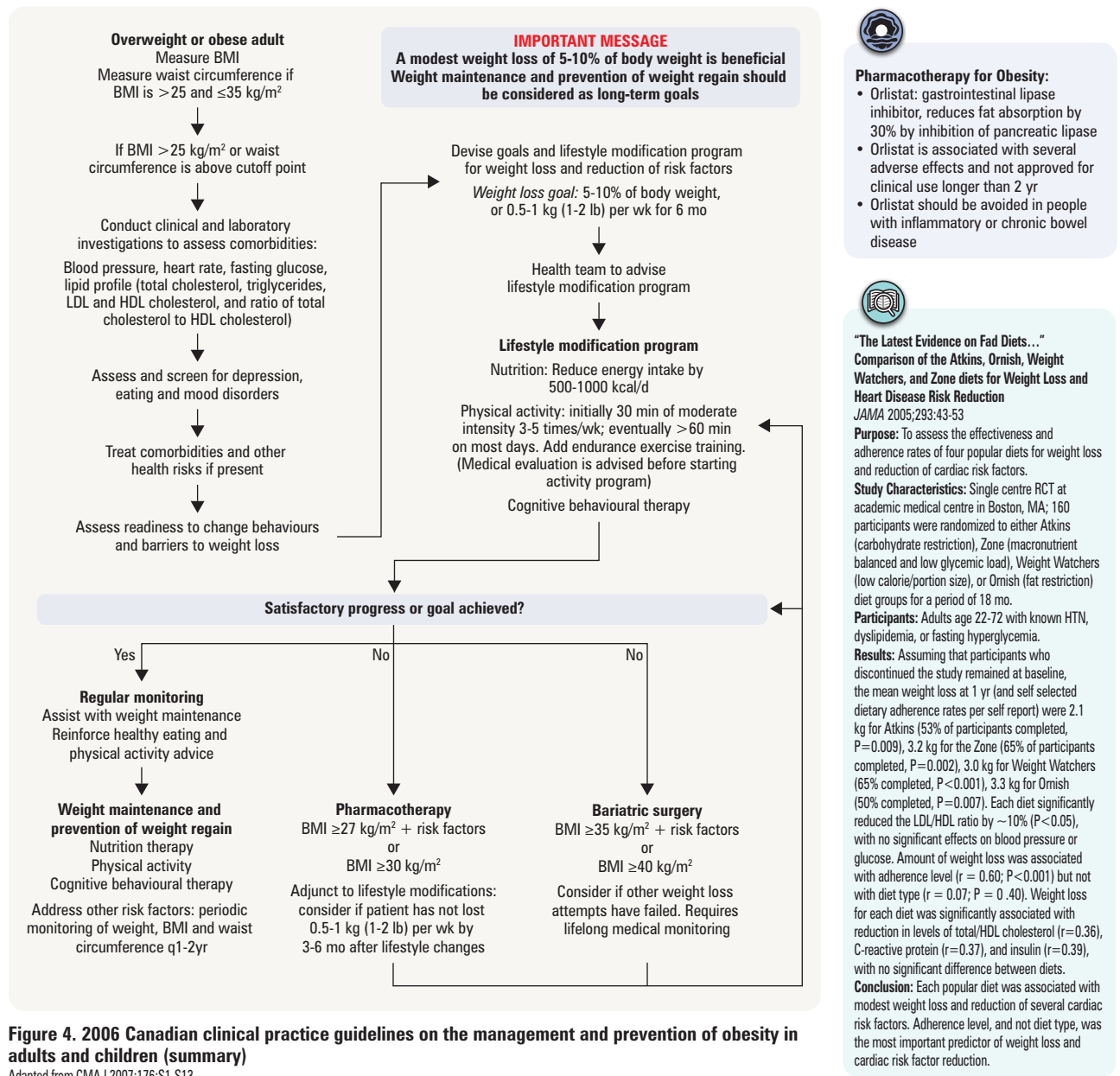
**Table 7. Classification of Weight by BMI, Waist Circumference, and Associated Disease Risks in Adults**

	BMI (kg/m <sup>2</sup> )	Obesity Class	Men ≤102 cm (40 in) Women ≤88 cm (35 in)	Men >102 cm (40 in) Women >88 cm (35 in)
Underweight	<18.5			
Normal	18.5-24.9			
Overweight	25.0-29.9		Increased	High
Obesity	30.0-34.9	I	High	Very High
	35.0-39.9	II	Very High	Very High
Extreme Obesity	40.0 +	III	Extremely High	Extremely High

From: Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks, National Institute of Health, National Heart Lung and Blood Institute, Obesity Education Initiative, [http://www.nhlbi.nih.gov/health/public/heart/obesity/lose\\_wt/bmi\\_dis.htm](http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm)

### Epidemiology

- 16% (4 million) of people ≥18 yr old are obese, 32% (8 million) are overweight in Canada, according to StatsCan (2007)
- obesity rate in people of aboriginal origin is 1.6 times higher than the national average
- proportion of children aged 6-11 who are overweight has more than doubled in the last 25 yr; percentage of overweight adolescents has tripled
- overweight and obesity rates in children are directly proportional to screen time (see *Exercise*, FM10)
- only 10-15% of population consume <30% fat daily
- obese persons generally consume more energy-dense food which tends to be highly processed, micronutrient poor, and high in fats, sugars, or starch



**Figure 4. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children (summary)**

Adapted from CMAJ 2007;176:S1-S13

## Dyslipidemia

- see [Endocrinology](#), E2
- defined as abnormal elevation of plasma cholesterol or triglyceride levels
- increased risk associated with obesity, DM, alcohol use

### Assessment

- measure fasting serum TC, LDL-C, HDL-C, and TG
- screen with full fasting lipid profile q1-3yr in males over age 40, females over age 50 or who are menopausal, or any adults with additional CAD risk factors
- assess for presence of other CAD risk factors
- screen for secondary causes: hypothyroidism, chronic kidney disease, DM, nephrotic syndrome, liver disease
- risk category
  - estimate using the model for 10-yr CAD risk developed from the Framingham data (Framingham Risk Score – FRS)
    - FRS calculated based on the following factors: gender, age, HDL-C, total cholesterol, sBP, smoking, diabetes
      - to be completed for men age 40-75, and women age 50-75 q3-5yr



### Hyperlipidemia Signs

- Atheromata: plaques in blood vessel walls
- Xanthoma: plaques or nodules composed of lipid-laden histiocytes in the skin (especially the eyelids)
- Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
- Corneal arcus (arcus senilis): lipid deposit in cornea



LDL cannot be calculated when TG  $\geq 4.5$  mmol/L.



- ♦ cardiovascular age calculated as patient's age  $\pm$  the difference between his or her estimated remaining life expectancy
  - used to increase adherence to therapy and reaffirm positive effect of following therapy
- primary target of therapy is LDL-C levels; the alternate primary targets are apolipoprotein B (apo B) and non-HDL-C (not used widely yet) (see Table 8)
- optional secondary targets once LDL-C/apo B is at target include TC:HDL-C ratio, apo B:apo AI ratio, hs-CRP (used more for risk stratification of CAD), non-HDL-C and serum TG levels
- emerging risk factors (from Framingham group)
  - lipoprotein a
  - metabolic syndrome
  - genetic risk
  - hormone replacement therapy
  - infectious agents

**Table 8. Target Lipid Values for Primary Prevention of CAD (2012 Canadian Cholesterol Guidelines)**

Risk Category	Initiate Treatment if:	Primary Targets	
		LDL-C	Alternate
High (FRS $\geq 20\%$ , or history of DM, CAD, PVD, atherosclerosis)	Consider treatment in all patients	<2 mmol/L or $\geq 50\%$ decrease in LDL-C	apo B <0.80 g/L $\leq 2.6$ mmol/L
Moderate (FRS 10-19%)	LDL-C $\geq 3.5$ mmol/L For LDL-C <3.5 consider if: apo B $\geq 1.2$ g/L or non-HDL-C $\geq 4$ mmol/L	<2 mmol/L or $\geq 50\%$ decrease in LDL-C	apo B <0.80 g/L non HDL-C $\leq 2.6$ mmol/L
Low (FRS $\leq 10\%$ )	LDL-C $\geq 5.0$ mmol/L Familial hypercholesterolemia	$\geq 50\%$ decrease in LDL-C	

Anderson TJ, et al. 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult. Can J Cardiol 2013; 29:151-167

## Management

- intensity and type of treatment is guided by “risk category” assigned
- 1. health behaviours (can decrease LDL-C by up to 10%)
  - smoking cessation: probably the most important for preventing CAD
  - dietary modification: reduce saturated fats, refined sugars, alcohol; increase fruits, vegetables and fibres
  - physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per wk
  - employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high risk patient should start treatment immediately with concurrent health behaviour interventions
- 2. pharmacologic therapy (can decrease LDL-C by up to 40%)
  - for a comparison of dyslipidemia medications, see [Endocrinology](#), E5
  - statins (HMG-CoA reductase inhibitors)
    - ♦ currently recommended as 1<sup>st</sup> line monotherapy following unsuccessful lifestyle modifications
    - ♦ risks: myopathy and hepatotoxicity – must follow LFTs q6-12mo
  - other agents: bile acid sequestrants, nicotinic acid, fibrates, psyllium, cholesterol absorption inhibitors (e.g. ezetimibe)
- after initiating drug therapy
  - monitor ALT, AST, CK at baseline then 6 wk later for signs of transaminitis or myositis; tolerate rise in CK up to 10 times upper limit of normal (2-3 times upper limit of normal if symptomatic), or serum creatinine of  $\leq 25\%$ ; repeat ALT, AST and CK with lipid bloodwork
  - fasting lipids should be measured at 3 mo
  - if adequate response is achieved, evaluate fasting lipids q6-12mo
- isolated hypertriglyceridemia (does not increase your cardiovascular risk!)
  - normal HDL-C and TC, elevated TG
  - mild  $\geq 2.2$  mmol/L ( $\geq 200$  mg/dL); marked  $\geq 5.6$  mmol/L ( $\geq 500$  mg/dL)
  - principal therapy is lifestyle modification
    - ♦ weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in diabetics, increased omega-3 fatty acid intake
  - drug therapy
    - ♦ nicotinic acid
    - ♦ fibrates



### Clinical Definition of Metabolic Syndrome

- Central obesity:
  - Men – waist circumference  $\geq 94$  cm
  - Women – waist circumference  $\geq 80$  cm
- Plus any TWO of the following four factors:

Risk Factor	Defining Level
TG level	$\geq 1.7$ mmol/L (150 mg/dL)
HDL-C level:	
Men	<1.0 mmol/L (40 mg/dL)
Women	<1.3 mmol/L (50 mg/dL)
Blood pressure	$\geq 130/85$ mmHg
Fasting glucose level	$\geq 5.6$ mmol/L (100 mg/dL)



To calculate Framingham Risk Score, go to <http://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#>



Use with caution when prescribing combined statin and fibrate therapy as there has been concern regarding the safety of certain combinations.



### Statin-Related Adverse Events: A Meta-analysis

*Clin Ther* 2006;28:26-35

**Study:** Meta-analysis of 18 RCTs (N=71,108) focused on adverse effects of statins.

**Patients:** Those taking statin monotherapy for primary or secondary prevention of CVD.

**Intervention:** Statin vs. placebo.

**Main outcome:** Adverse events (AE) including elevated liver enzymes or myopathy (myalgias, elevated CK, rhabdomyolysis).

**Results:** Statin therapy increased the risk of any AE by 39% (OR = 1.4; 95% CI, 1.09-1.80; P = 0.008) compared with placebo. Treating 1000 patients with a statin would cause 5 AE. Serious events (CK > 10 times the upper limit of normal or rhabdomyolysis) are infrequent (NNH = 3400) and rhabdomyolysis, although serious, is rare (NNH = 7428).

**Conclusion:** Statin therapy was associated with greater odds of AEs compared with placebo but with substantial clinical benefit. Similar rates of serious AEs were observed between statin and placebo.



### The Benefits of Statins in People without Established Cardiovascular Disease but with Cardiovascular Risk Factors: Meta-Analysis of Randomized Controlled Trials

*Brit Med J* 2009;338:b2376

**Study:** Meta-analysis of 10 RCTs.

**Population:** 70,388 participants (minimum of 80% without established cardiovascular (CV) disease).

**Intervention:** Statins, placebo, active control, usual care.

**Main outcome:** All-cause mortality. Other outcomes: major coronary events, major cerebrovascular events.

**Results:** Statin use significantly reduced the incidence of all-cause mortality (OR 0.88; 95% CI 0.81-0.96), major coronary events (OR 0.70; 95% CI 0.61-0.81) and major cerebrovascular events (OR 0.81; 95% CI 0.71-0.93).

**Conclusion:** Statins largely reduce the risk of major CV events and improve survival in patients with CV risk factors without established CV disease.



## Exercise

### Epidemiology

- 25% of the population exercises regularly, 50% occasionally, 25% are sedentary
- screen time (time spent watching TV/movies, playing video games, or using the computer) has been increasing steadily in the last several yr, while time spent being physically active has been decreasing
- current recommendation from international pediatric societies is that children (>2 yr old) should limit their screen time to less than 2 h/d

### Management

- assess current level of fitness, motivation and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, diabetes (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- Canadian Physical Activity Guidelines for adults age 18-64 (ParticipACTION)
  - ≥150 min of moderate- to vigorous-intensity aerobic physical activity per wk, in bouts of ≥10 min
    - ♦ moderate-intensity: brisk walking, bike riding
    - ♦ vigorous-intensity: jogging, cross-country skiing
  - muscle and bone strengthening activities using major muscle groups, ≥2 d/wk
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, type 2 diabetes, osteoporosis, overweight/obesity
  - leads to improved fitness, strength, and mental health (morale and self-esteem)

## Smoking Cessation

### Epidemiology

- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2008 Canadian data from the Canadian Tobacco Use Monitoring Survey (CTUMS) on population age 15 or older
  - 18% are current smokers (lowest since 1965)
  - highest prevalence in age group 20-24 (28%)
  - 15% of youth age 15-19 smoke (decreased from 25% in 2000): more males smoke than females; number of cigarettes consumed per day also decreasing

### Management

- general approach
  - identify tobacco users; elicit smoking habits, previous quit attempts and results
  - every smoker should be offered treatment
  - make patient aware of withdrawal symptoms
    - ♦ low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
  - ≥4 counselling sessions >10 min each with 6-12 mo follow-up yields better results
  - 14% abstinent with counselling vs. 10% without counselling
  - approach depends on patient's stage of change (see *Motivational Strategies for Behavioural Change*, FM5)
- willing to quit
  - follow the 5 As (see sidebar)
  - provision of social support, community resources
  - pregnant patients: advise to quit first without pharmacotherapy. Nicotine replacement therapy (NRT) should be made available to pregnant women who are unable to quit using non-pharmacologic methods; nicotine patches are strongly encouraged. Use bupropion (no evidence of fetal or reproductive harm) only if benefits > risks; consult Motherisk. Varenicline has not been studied in pregnancy and should not be used in pregnant women
- pharmacologic therapy
  1. nicotine replacement therapy
    - 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
    - no difference in achieving abstinence for different forms of NRT
    - reduces cravings and withdrawal symptoms without other harmful substances that are contained in cigarettes
    - use with caution: immediate post-MI, serious/worsening angina, serious arrhythmia



#### Physician Advice for Smoking Cessation

*Cochrane DB Syst Rev* 2008;2:CD000165

This systematic review of 17 trials compared brief advice by the physician versus no advice.

**Reviewers' conclusions:** Simple advice can increase cessation rates by 1-3%. More intensive advice and providing follow-up support may further increase the quit rates.



#### Assist Patient in Developing Quit Plan

##### STAR

**Set** quit date

**Tell** family and friends (for support)

**Anticipate** challenges (e.g. withdrawal)

**Remove** tobacco-related products (e.g. ashtrays/lighters)



#### The 5 As for Patients Willing to Quit

**Ask** if patient smokes

**Advise** patient to quit

**Assess** willingness to quit

**Assist** in quit attempt

**Arrange** follow-up

2. Bupropion SR (Zyban®)
  - 21% abstinent at 12 mo vs. 8% for placebo
3. Varenicline (Champix®)
  - partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce the response to smoked nicotine)
  - more effective than bupropion (23% abstinent from 9-52 wk with varenicline vs. 16% for bupropion vs. 9% with placebo)

**Table 9. Types of Nicotine Replacement Therapy**

Type	Dosage	Comment	Side Effects
<b>Nicotine Gum (OTC)</b>	2 mg if <25 cig/d 4 mg if >25 cig/d 1 piece q1-2h for 1-3 mo (max 24 pieces/d)	Chew until "peppery" taste then "park" between gum and cheek to facilitate absorption Continue to chew-park intermittently for 30 min	Mouth soreness Hiccups Dyspepsia Jaw ache Most are transient
<b>Nicotine Patch (OTC)</b>	Use for 8 wk 21 mg/d x 4 wk 14 mg/d x 2 wk 7 mg/d x 2 wk	Start with lower dose if <10 cig/d Change patch q24h and alternate sides	Skin irritation Insomnia Palpitations Anxiety
<b>Nicotine Inhaler (OTC)</b>	6-16 cartridges/d for up to 12 wk	Nicotine inhaled through mouth, absorbed in mouth and throat not in lungs	Local irritation Coughing
<b>Nicotine Nasal Spray (Rx)</b>		Newer form of NRT	Local irritation, coughing

**Table 10. Bupropion as Treatment for Smoking Cessation**

Mechanism	Dosage	Prescribing*	Contraindications
Inhibits re-uptake of dopamine and/or norepinephrine • Side effects: insomnia, dry mouth	1. 150 mg qAM x 3 d 2. Then 150 mg bid x 7-12 wk 3. For maintenance consider 150 mg bid for up to 6 mo	1. Decide on a quit date 2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk)	Seizure disorder Eating disorder MAOI use in past 14 d Simultaneous use of bupropion (Wellbutrin®) for depression

\*May be used in combination with nicotine replacement therapy

**Table 11. Varenicline as Treatment for Smoking Cessation**

Mechanism	Dosage	Prescribing*	Contraindications
Partial nicotinic receptor agonist, and partial nicotinic receptor competitive antagonist • Side effects: nausea, vomiting, constipation, headache, dream disorder, insomnia, increased risk of psychosis, depression, suicidal ideation	1. 0.5 mg qAM x 3 d 2. Then 0.5 mg bid x 4 d 3. Continue 1 mg bid x 12 wk ± additional 12 wk as maintenance	1. Decide on a quit date 2. Continue to smoke for first wk of treatment and then completely stop	Caution with pre-existing psychiatric condition

\*May be used in combination with nicotine replacement therapy

- unwilling to quit
  - motivational intervention (5 Rs) (see sidebar):
    1. Relevance to patient
      - ♦ relevant to patient's disease status or risk, family or social situation (e.g. having children in the home), health concerns, age, gender
    2. Risks of smoking
      - ♦ short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
      - ♦ long-term: MI, stroke, COPD, lung CA, other cancers
      - ♦ environmental: higher risk in spouse/children for lung CA, SIDS, asthma, respiratory infections
    3. Rewards: benefits
      - ♦ improved health, save money, food tastes better, good example to children
    4. Roadblocks: obstacles
      - ♦ fear of withdrawal, weight gain, failure, lack of support
    5. Repetition
      - ♦ reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)



#### Nicotine Replacement Therapy for Smoking Cessation

*Cochrane DB Syst Rev* 2008;1:CD000146  
This systematic review of 132 randomized trials compared NRT to placebo or no treatment or compared different NRT doses.

**Reviewers' conclusions:** All commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) are effective as part of a strategy to promote smoking cessation. They increase the rate of quitting by 50-70% regardless of setting and independent on the level of additional support provided to the smoker. Compared to a single form of NRT, combining a nicotine patch with a rapid delivery form of NRT may be more effective.



#### Antidepressants for Smoking Cessation

*Cochrane DB Syst Rev* 2007;1:CD000031  
This systematic review of 66 randomized trials compared antidepressant medication to placebo or alternative pharmacotherapy for smoking cessation and where follow-up was longer than 6 mo.

**Reviewers' conclusions:** The antidepressants bupropion and nortriptyline can aid smoking cessation and have a similar efficacy to NRT. Compared to bupropion, varenicline showed higher quit rates. SSRIs (e.g. fluoxetine) or venlafaxine did not have a significant effect.



#### The 2-3 Pattern of Smoking Cessation

- Onset of withdrawal is 2-3 h after last cigarette
- Peak withdrawal is at 2-3 d
- Expect improvement of withdrawal symptoms at 2-3 wk
- Resolution of withdrawal at 2-3 mo
- Highest relapse rate within 2-3 mo



#### The 5 Rs for Patients Unwilling to Quit

**Relevance to patient** (health concerns, family/social situations)  
**Risks of smoking**  
**Rewards of quitting**  
**Roadblocks to quitting**  
**Repetition of motivational intervention at each visit**

- recent quitter
  - highest relapse rate within 3 mo of quitting
    - ♦ minimal practice: congratulate on success, encourage ongoing abstinence, review benefits and problems
    - ♦ prescriptive interventions: address problem of weight gain, negative mood, withdrawal, lack of support

## Alcohol

- see [Psychiatry](#), PS22

### Definition

- diagnostic categories occur along a continuum (see Figure 5)

### Epidemiology

- 10-15% of patients in family practice are problem drinkers
- 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
- more likely to miss diagnosis in women, elderly, patients with high socioeconomic status

### Assessment

- screen for alcohol dependence with CAGE questionnaire (see sidebar)
  - if CAGE positive, explore with further questions for alcohol abuse/dependence
- assess drinking profile
  - setting, time, place, occasion, with whom
  - impact on: family, work, social
  - quantity-frequency history
    - ♦ how many drinks per day?
    - ♦ how many days per week?
    - ♦ maximum number of drinks on any one day in the past month?
- if identified positive for alcohol problem
  - screen for other drug use
  - identify medical/psychiatric complications
  - ask about drinking and driving
  - ask about past recovery attempts and current readiness for change

### Investigations

- GGT and MCV for baseline and follow-up monitoring
- AST, ALT (usually AST:ALT approaches 2:1 in an alcoholic)
- CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by liver)

### Management

- intervention should be consistent with patient's motivation for change
- regular follow-up is crucial
- 10% of patients in alcohol withdrawal will have seizures or delirium tremens
- Alcoholics Anonymous/12-steps program
  - outpatient/day programs for those with chronic, resistant problems
  - family treatment (Al-Anon, Alateen, screen for spouse/child abuse)
- in-patient program if
  - dangerous or highly unstable home environment
  - severe medical/psychiatric problem
  - addiction to drug that may require in-patient detoxification
  - refractory to other treatment programs
- pharmacologic
  - diazepam for withdrawal
  - disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, nausea/vomiting, hypotension if alcohol is ingested (available in U.S., but no longer available in Canada)
  - naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
    - ♦ may trigger withdrawal in opioid-dependent patients

### Prognosis

- relapse is common and should not be viewed as failure
- monitor regularly for signs of relapse
- 25-30% of abusers exhibit spontaneous improvement over 1 yr
- 60-70% of individuals with jobs and families have an improved quality of life 1 yr post-treatment

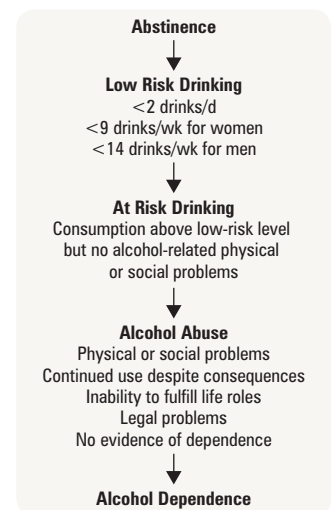


Figure 5. Continuum of alcohol use



#### Standard Drink Equivalents

- One standard drink = 14 g of pure alcohol
- Beer (5% alcohol) = 12 oz
  - Wine (12-17% alcohol) = 5 oz
  - Fortified wine = 3 oz
  - Hard liquor (80 proof) = 1.5 oz



#### CAGE Questionnaire

- C** Have you ever felt the need to **CUT** down on your drinking?
- A** Have you ever felt **ANNOYED** at criticism of your drinking?
- G** Have you ever felt **GUILTY** about your drinking?
- E** Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (**EYE OPENER**)

≥2 for men or ≥1 for women suggests possibility of problem drinking (sensitivity 85%, specificity 89%)



#### Alcohol Metabolized per Hour

- Alcohol metabolism is constant (zero-order kinetics) regardless of blood alcohol level (BAL)
- Average metabolism ranges between 13-25 mg/dL blood/h or 100-200 mg/kg/h
- Equivalent to metabolizing 0.5-1 standard drink per hour or BAL decrease of 0.01% per hour
- Metabolism more rapid in chronic alcoholics



#### Some Adverse Medical Consequences of Problem Drinking

- GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/esophageal cancer
- Cardiac: hypertension, alcoholic cardiomyopathy
- Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
- Hematologic: anemia, coagulopathies
- Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage

# Common Presenting Problems

## Abdominal Pain

- see [Gastroenterology](#), G4 and [General Surgery](#), GS4

### Epidemiology

- 20% of individuals have experienced abdominal pain within the last 6-12 mo
- 90% resolve in 2-3 wk
- only 10% are referred to specialists, of those <10% admitted to hospital

### Etiology

- most common diagnosis is “nonspecific abdominal pain,” which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: toxic ingestion, foreign body, psychogenic

### Pathophysiology

- type of pain
  - somatic pain: sharp, localized pain
  - visceral pain: dull, generalized pain
- location of pain
  - epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
  - periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon
  - hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region

### Investigations

- guided by findings on history and physical
- possible bloodwork: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, tox screen,  $\beta$ -hCG
- imaging
  - CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  - abdominal x-ray, KUB (consider: gas pattern, free air, kidney stones, constipation)
  - ultrasound (gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  - CT scan (AAA, appendicitis)
- other tests
  - urinalysis
  - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
  - *H. pylori* testing (urea breath test, serology, biopsy)



#### Key Questions on History

- OPQRST
- Location of pain (see [General Surgery](#), GS4)
- Symptoms of peritonitis
- Associated symptoms (nausea, vomiting, fever, chills, weight loss, bowel movements, diarrhea, melena, hematochezia, urinary symptoms)
- Gynecological history (pregnancy, infection, menstrual history, discharge)
- Past surgical history
- Medications (NSAIDs, antibiotics, alcohol)



In patient age > 50, keep a high index of suspicion for AAA – its presentation may mimic renal colic or diverticulitis.



If pain precedes nausea/vomiting, cause of abdominal pain is more likely to be surgical.



#### Abdominal Pain Red Flags:

- Severe pain
- Signs of shock
- Peritoneal signs
- Abdominal distention
- Pain out of proportion to clinical findings



## Allergic Rhinitis

- see [Otolaryngology](#), OT23

### Definition

- inflammation of the nasal mucosa that is triggered by an allergic reaction
- classification:
  - seasonal
    - ♦ symptoms during a specific time of the year
    - ♦ common allergens: trees, grass and weed pollens, airborne moulds
  - perennial
    - ♦ symptoms throughout the year with variation in severity
    - ♦ common allergens: dust mites, animal dander, moulds

### Etiology

- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

### Epidemiology

- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, sinusitis, and otitis media

### Assessment

- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

### Management

- conservative
  - minimize exposure to allergens
    - ♦ most important aspect of management, often sufficient (may take months)
  - maintain hygiene, saline nasal rinses
- pharmacologic agents
  - oral antihistamines – first line therapy for mild symptoms
    - ♦ e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  - intranasal corticosteroids for moderate/severe or persistent symptoms (>1 mo of consistent use to see results)
  - intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)
- allergy skin testing
  - for patients with chronic rhinitis
  - symptoms not controlled by allergen avoidance, pharmacological therapy
  - may identify allergens to include in immunotherapy treatment
- immunotherapy (allergy shots)
  - reserved for severe cases unresponsive to pharmacologic agents
  - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic



#### Differential Diagnosis

- Acute viral infection
- Vasomotor rhinitis
- Deviated septum
- Nasal polyps
- Acute/chronic sinusitis
- Drug-induced rhinitis



**Rhinitis medicamentosa:** Rebound nasal congestion. Occurs with prolonged use (> 5-7 d) of vasoconstrictive intranasal medications. Patient may become dependent, requiring more frequent dosing to achieve the same decongestant effect.

## Amenorrhea

- see [Gynecology](#), G12



### Definition and Etiology

- classified as primary or secondary
  - primary
    - ♦ absence of menstruation by age 14 in women without secondary sexual characteristics or absence of menstruation by age 16 in women with secondary sexual characteristics
    - ♦ causes: Turner's syndrome, constitutional delay of growth and puberty, Kallmann syndrome, androgen insensitivity syndrome, Müllerian agenesis, imperforate hymen, transverse vaginal septum, + causes of secondary amenorrhea
  - secondary
    - ♦ absence of menstruation for 3 mo in women with previously normal menstruation, or absence of menstruation for 9 mo in women with previous oligomenorrhea
    - ♦ causes: pregnancy, hypothyroidism, hyperprolactinemia, medications, premature ovarian failure, anorexia or bulimia nervosa, CNS tumour, chronic illness, PCOS

### Assessment

- history
  - menarche and menstrual history, sexual activity, exercise, weight loss, current or previous chronic illness, prescription/illicit drug use, previous CNS chemotherapy or radiation, previous pelvic radiation, psychosocial stressors
  - family history of: genetic defects, infertility, menarche and menstrual history, pubertal history
- physical
  - growth chart, BMI, Tanner staging, dysmorphic features (e.g. webbed neck, short stature), signs of Cushing's disease, thyroid exam, hirsutism or acne, pubic hair pattern, imperforate hymen, absent uterus

### Investigations

- based on clinical picture
- consider  $\beta$ -hCG, prolactin, TSH, progesterone challenge test, FSH and LH levels, pelvic ultrasound, MRI brain, karyotype

## Anxiety

- see [Psychiatry](#), PS13



### Epidemiology

- 25-30% of patients in primary care settings have psychiatric disorders
- many are undiagnosed or untreated; hence the need for good screening
- high rate of coexistence of anxiety disorders and depression

### Screening

- screening questions:
  - Do you tend to be an anxious or nervous person?
  - Have you felt unusually worried about things recently?
  - Has this worrying affected your life? How?
- if positive response, follow up with symptom-specific questions (see Figure 6)

### Assessment

- associated symptoms
- risk factors
  - family history of anxiety or depression, past history of anxiety, stressful life event, social isolation, female gender, co-morbid psychiatric diagnosis (e.g. depression)
- assess substance abuse, co-morbid depression, suicidal ideation/self-harm
- to differentiate anxiety disorders, consider symptoms and their duration (see Figure 6)



### Differential Diagnosis of Anxiety Disorders (see Figure 6)

- Panic disorder
- GAD
- PTSD
- OCD
- Social phobia
- Specific phobia
- Separation anxiety (children)
- Other: GMC, mood disorder, psychotic disorder



### Rule Out

- Cardiac (post MI, arrhythmias)
- Endocrine (hyperthyroidism, diabetes, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatoform disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (OCPD)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/benzodiazepine withdrawal)

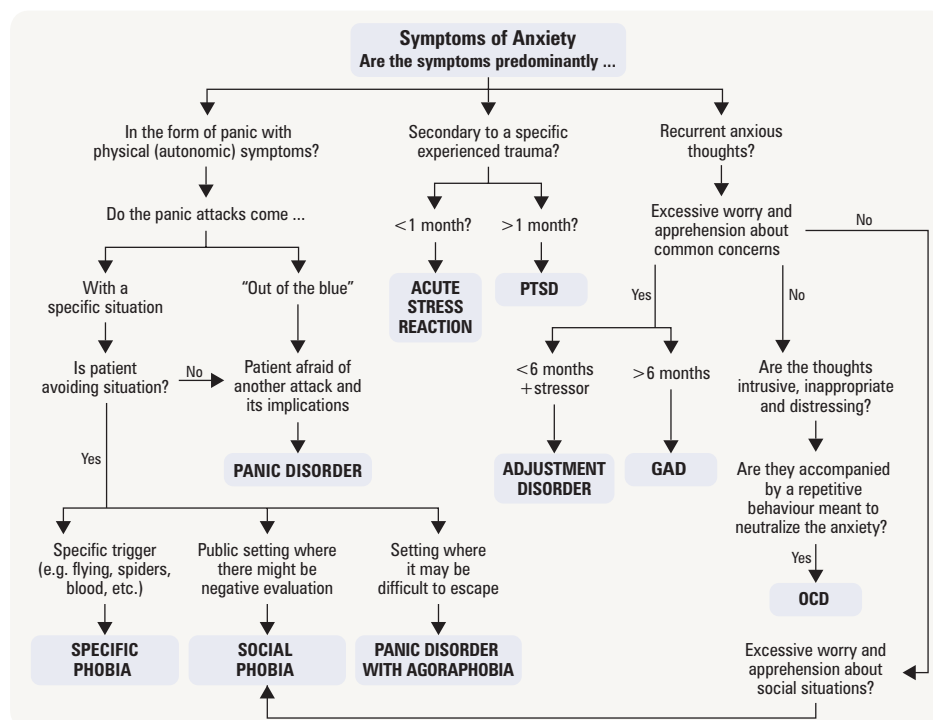


### Symptoms of GAD

#### AND I C REST

- Anxious, nervous, or worried
- No control over the worry
- Duration > 6 mo
- Irritability
- Concentration impairment
- Restlessness
- Energy decreased
- Sleep impairment
- Tension in muscles

Can Fam Physician 2005;51:1340-1342



**Figure 6. Differentiating anxiety disorders**

Adapted from: Evans M, Bradwejn J, Dunn L. Anxiety Review Panel. Guidelines for the treatment of anxiety disorders in primary care. Toronto: Queen's Printer of Ontario, 2000. p41

### Management

- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- lifestyle advice: decrease caffeine and alcohol intake, exercise, relaxation techniques, mindfulness strategies
- self-help materials, community resources (e.g. support groups)
- cognitive behavioural therapy: cognitive interventions, exposure therapy, etc.
- for pharmacotherapy, see [Psychiatry](#), PS48





## Asthma/COPD

- see [Respirology](#), R6

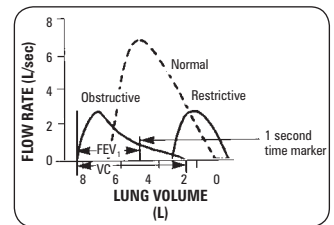
### Definition

- asthma
  - chronic but reversible airway inflammation characterized by periodic attacks of wheezing, shortness of breath, chest tightness, and coughing
  - airways hyper-responsive to triggers/antigens leading to acute obstructive symptoms by bronchoconstriction, mucous plugs and increased inflammation
  - cannot be diagnosed at first presentation; called reactive airway disease until recurrent presentations
  - pulmonary function tests (PFTs) can be done from age 6 or when child able to follow instructions to do PFTs
  - peak flow meters are useful in the office and at home for monitoring
- chronic obstructive pulmonary disease (COPD)
  - a group of chronic, progressive, expiratory lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
  - emphysema and chronic bronchitis are the most common forms of COPD

**Table 12. Differentiating COPD from Asthma**

	COPD	Asthma
<b>Age of Onset</b>	Usually in 6th decade	Any age (but 50% of cases diagnosed in children age <10)
<b>Role of Smoking</b>	>10 pack yr	Not causal, known trigger
<b>Reversibility of Airflow Obstruction</b>	Airflow obstruction is chronic and persistent	Airflow obstruction is episodic and usually reversible with therapy
<b>Evolution</b>	Slow, progressive worsening (with periodic exacerbations)	Stable, episodic, less than 50% will outgrow
<b>History of Allergy</b>	Infrequent	Over 50% patients
<b>Precipitators</b>	Environmental irritants (air pollution), cigarette smoking, $\alpha$ -1 antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs)	Environmental irritants (dust, pollen), animal fur, cold air, exercise, URTIs, cigarette smoke, use of $\beta$ -blockers/ASA
<b>Symptoms/Signs</b>	Chronic cough, sputum and/or dyspnea	Wheeze (hallmark symptom), dyspnea, chest tightness, cough which is worse in cold, at night, and in early AM, prolonged expiration
<b>Diffusion Capacity</b>	Decreased (more so in pure emphysema)	Normal (for pure asthma)
<b>Hypoxemia</b>	Chronic in advanced stages	Not usually present Episodic with severe attacks
<b>Spirometry</b>	May have improvement with bronchodilators but not universally seen	Marked improvement with bronchodilators or steroids
<b>Chest X-ray</b>	Often normal Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist, bullae	Often normal or episodic hyperinflation Hyperinflation during asthma attack
<b>Management</b>	<b>Mild</b> Step 1: SABA prn (salbutamol) Step 2: SABA prn + LAAC (i.e. tiotropium) or + LABA (e.g. salmeterol) <b>Moderate</b> Step 3: SABA prn + LAAC + low-dose combined ICS/LABA; consider inhaled vs. oral steroids <b>Severe</b> Step 4: $\pm$ theophylline Pneumococcal vaccination, annual influenza immunization	Ongoing patient education, and environmental control SABA taken prn as rescue medication + maintenance meds Maintenance medications: Step 1: Low-dose ICS Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LT modifier, or long-acting theophylline Step 3: Medium/high-dose ICS plus either LABA, LT modifier, or long-acting theophylline Step 4: As above plus immunotherapy $\pm$ oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization

SABA = short-acting  $\beta$ -agonist; LAAC = long-acting anticholinergic; LABA = long-acting  $\beta$ -agonist; ICS = inhaled glucocorticosteroids; LT modifier = leukotriene modifier



**Figure 7. Expiratory flow volume curves (obstructive, normal and restrictive disease)**

See also [Respirology](#), R4. Adapted from Weinberger SE. Principles of pulmonary medicine, 5th ed. With permission from Elsevier. ©2008.



### What Colour is Your Inhaler?

Name	Body/Cap Colour
<b><math>\beta_2</math>-agonists</b>	
Salbutamol – Ventolin®	light blue/navy
Salmeterol – Serevent®	teal/light teal
Terbutaline – Bricanyl®	blue/white
<b>ICS</b>	
Fluticasone – Flovent®	orange/peach
Budesonide – Pulmicort®	white/brown
<b>Combined long-acting <math>\beta_2</math>-agonist + ICS</b>	
Fluticasone/Salmeterol – purple discus Advair®	purple discus
Budesonide/Formoterol – red/white Symbicort®	red/white
Ipratropium/Albuterol – clear/orange Combivent®	clear/orange
<b>Anticholinergics</b>	
Ipratropium – Atrovent®	clear/green
Tiotropium – Spiriva®	white/turquoise



### More about Inhalers:

- Aerosols (puffers=MDI, MDI + spacer)
  - MDIs should be used with spacers to:
    - Reduce side effects
    - Improve amount inhaled
    - Increase efficiency of use
- Dry powder Inhaler (discus, turbuhaler and diskhaler), they require deep and fast breathing (may not be ideal for children)
- Nebulizers can be used to convert liquid medications into a fine mist: recommended for use if contraindications to MDIs



### Differential Diagnosis of Wheezing

- Allergies, anaphylaxis
- Asthma, reactive airway disease
- Gastroesophageal reflux disease
- Infections (bronchitis, pneumonia)
- Obstructive Sleep Apnea
- COPD
- Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction



When prescribing salbutamol, watch out for signs of **hypokalemia**: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, nausea, vomiting, polyuria.

## Benign Prostatic Hyperplasia (BPH)

- see [Urology](#), U8

### Definition

- hyperplasia of the stroma and epithelium in the periurethral transition zone

### History and Physical

- include current/past health, surgeries, trauma, current and OTC meds
- specific urinary symptoms (see Table 13)
- physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth and rubbery in BPH)

### Investigations

- urinalysis to exclude UTI and for microscopic hematuria (common sign)
- serum PSA: protein produced by prostatic tissue, see [Urology](#), U25
  - values:
    - ♦ <4.0 ng/mL: normal, but must take into account patient's age and velocity of PSA increase
    - ♦ 4-10 ng/mL: consider measuring free/total PSA
    - ♦ >10 ng/mL: high likelihood of prostate pathology
  - PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI
  - increased PSA in a younger man is more often due to cancer than other causes
  - abnormal DRE or PSA should trigger further assessment
  - discuss test with men at increased risk of prostate cancer (FHx, African ancestry) or who are concerned about development of prostate cancer
  - decision to test PSA in an asymptomatic man should involve discussion about the risks and possible benefits
- other tests:
  - Cr, BUN
  - post-void residual volume by ultrasound
  - urodynamic studies, renal ultrasound
  - patient voiding diary
- tests NOT recommended as part of routine initial evaluation include:
  - cystoscopy
  - cytology
  - prostate ultrasound or biopsy
  - IVP

**Table 13. Symptoms and Complications of BPH**

Obstructive Symptoms	Irritative Symptoms	Late Complications
Hesitancy (difficulty starting urine flow)	Urgency	Hydronephrosis
Diminution in size and force of urinary stream	Frequency	Loss of renal concentrating ability
Stream interruption (double voiding)	Nocturia	Systemic acidosis
Urinary retention (bladder does not feel completely empty)	Urge incontinence	Renal failure
Post-void dribbling	Dysuria	
Overflow incontinence		
Nocturia		

### Management

- referral to urologist if moderate/severe symptoms
- conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
  - fluid restriction (avoid alcohol and caffeine)
  - avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
  - pelvic floor/Kegel exercises
  - bladder retraining (scheduled voiding)
- pharmacological: for moderate/severe symptoms
  - $\alpha$ -receptor antagonists [e.g. terazosin (Hytrin<sup>®</sup>), doxazosin (Cardura<sup>®</sup>), tamsulosin (Flomax<sup>®</sup>), alfuzosin (Xatral<sup>®</sup>)]
    - ♦ relaxation of smooth muscle around the prostate and bladder neck
  - 5- $\alpha$  reductase inhibitor [e.g. finasteride (Proscar<sup>®</sup>)]
    - ♦ only for patients with demonstrated prostatic enlargement due to BPH
    - ♦ inhibits enzyme responsible for conversion of testosterone into dihydrotestosterone (DHT) thus reducing growth of prostate



#### Self-Management Asthma and COPD Education and Written Action Plan:

- Education is a key component in management of asthma and COPD.
- Guided self-management combining education, regular medical review, self-assessment and written action plan have been shown to reduce hospitalizations, ER visits, and missed days at work or school.
- Sample action plans available online: <http://www.respiratoryguidelines.ca>



#### Signs of Poorly Controlled Asthma

- $\beta_2$  agonist use >4x/wk
- Asthma-related absence from work/school
- Exercise induced asthma
- Night-time symptoms >1x/wk



#### Differential Diagnosis

- Prostate cancer
- Urethral obstruction
- Bladder neck obstruction
- Neurogenic bladder
- Cystitis
- Prostatitis



#### Prostate-Cancer Mortality at 11 Years of Follow-up

NEJM 2012;366:981-90

**Study:** Updated "ERSPC" study – multicentre randomized trial of screening for prostate cancer using PSA.

**Patients:** 162,388 men, age 55-69 from 8 different European countries.

**Intervention:** PSA-based screening.

**Main Outcome:** Mortality from prostate cancer.

**Results:** In screening group, RRR = 21%, ARR = 1.07 deaths/1000 men, NNT = 1055 – therefore to prevent one death from prostate cancer, 1055 men would need to be screened.

- phytotherapy (e.g. saw palmetto berry extract, *Pygeum africanum*)
  - ♦ more studies required before this can be recommended as standard therapy
  - ♦ considered safe
- surgical:
  - TURP (transurethral resection of the prostate), TUIP (transurethral incision of the prostate, for prostates <30 g)
    - ♦ absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
    - ♦ complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido

## Bronchitis (Acute)

### Definition

- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

### Epidemiology

- 5th most common diagnosis in family medicine, most common is URTI

### Etiology

- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV)
- 20% bacterial: *M. pneumoniae*, *C. pneumoniae*, *S. pneumoniae*

### Investigations

- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not very informative
- CXR if suspect pneumonia (cough >3 wk, abnormal vital signs, localized chest findings) or CHF
- pulmonary function tests with methacholine challenge if suspect asthma

### Management

- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/d when febrile), humidity, analgesics and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
  - antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic (refer to *Antimicrobial Quick Reference*, FM53)
  - antibiotics in children show no benefit



#### Differential Diagnosis of Bronchitis

- URTI
- Asthma
- Acute exacerbation of chronic bronchitis
- Sinusitis
- Pneumonia
- Bronchiolitis
- Pertussis
- Environmental/occupational exposures
- Post-nasal drip
- Others: GERD, CHF, cancer, aspiration syndromes, CF, foreign body



#### How to Tell if Viral or Bacterial?

Bacterial infections tend to give a higher fever, excessive amounts of purulent sputum production, and may be associated with concomitant COPD. Note: purulent sputum is not necessarily bacterial.



#### Risk Factors for Coronary Artery Disease

##### Major

- Smoking
- Diabetes
- Hypertension
- Hyperlipidemia
- Family history of early CAD in first degree relative
- Untreated obstructive sleep apnea

##### Minor

- Obesity
- Sedentary lifestyle
- Age

## Chest Pain

- see [Cardiology and Cardiovascular Surgery](#), C4 and [Emergency Medicine](#), ER21

### Differential Diagnosis

**Table 14. Differential Diagnosis of Chest Pain**

Cardiac	Pulmonary	GI	MSK/Neuro	Psychologic
Angina*	Hemothorax*	Cholecystitis	Arthritis	Anxiety
Aortic dissection*	Lung CA	Esophageal spasm	Costochondritis	Depression
Endocarditis	PE*	GERD	Herpes zoster	Panic
MI*	Pneumonia	Hepatitis	Intercostal strain	
Myocarditis	Pneumothorax*	Perforated viscus*	Rib fractures	
Pericarditis*	Pulmonary HTN	PUD	Trauma	

\*Emergent

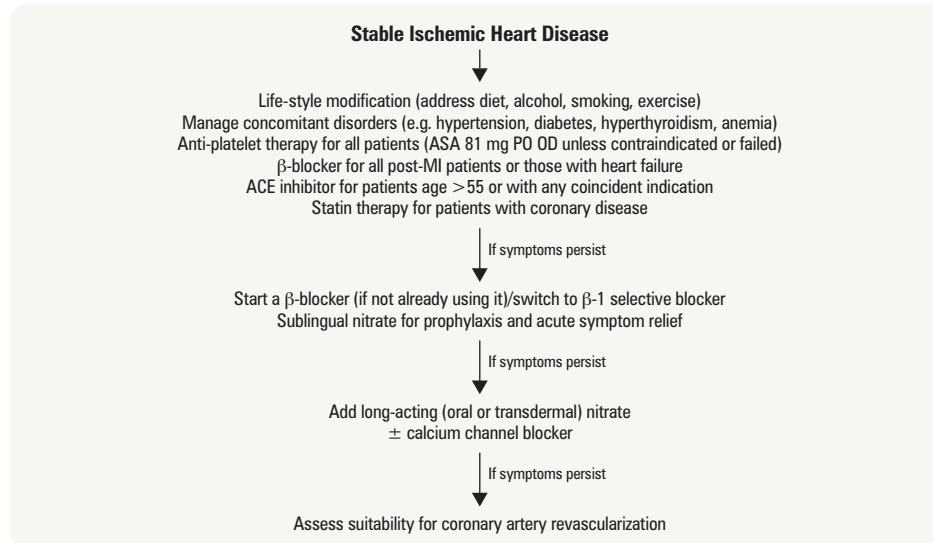
### Investigations

- ECG, CXR, and others if indicated (cardiac enzymes, D-dimers, liver function tests (LFTs), etc.)
- refer to ER if suspect serious etiology (e.g. aortic dissection, MI)

### Management of Common Causes of Chest Pain

- angina/ischemic heart disease
  - nitroglycerin (NTG): wait 5 min between sprays and if no effect after 3 sprays, send to ER
- myocardial infarction
  - ASA (162-325 mg, chewed), clopidogrel (Plavix\*), enoxaparin, morphine, oxygen, NTG

- $\pm$  reperfusion therapy with tissue plasminogen activator (tPA) or streptokinase (SK) if within 6 h (Note: can only use SK once in lifetime) or percutaneous intervention (cath lab)
- start  $\beta$ -blocker (e.g. metoprolol starting dose 12.5 mg PO OD and gradually increase dose, titrate to the HR rate goal of 60 bpm)
- endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results
- GERD: antacids,  $H_2$  blockers, PPIs, patient education
- costochondritis: NSAIDs



**Figure 8. Treatment algorithm for stable ischemic heart disease**

References: Ontario Program for Optimal Therapeutics. Ontario drug therapy guidelines for stable ischemic heart disease in primary care. Toronto: Queen's Printer of Ontario, 2000. p10

Recommendations of the Task Force of the European Society of Cardiology. Guidelines on the management of stable angina pectoris, 2006. p63



#### High-Risk Symptoms and Signs of Chest Pain include:

- Severe pain
- Pain for >20 min
- New onset pain at rest
- Severe SOB
- Loss of consciousness
- Hypotension
- Tachycardia
- Bradycardia
- Cyanosis



#### MI in Elderly Women

Elderly women can often present with dizziness, back pain, lightheadedness or weakness, in the absence of chest pain.



#### Common Cold Etiology

**PRIMA**  
Paramyxoviruses  
Rhinoviruses  
Influenza viruses  
Myxoviruses  
Adenoviruses



#### Influenza vs. Colds: A Guide to Symptoms

Features	Flu	Cold
Onset of illness	Sudden	Slow
Fever	High fever	None
Exhaustion level	Severe	Mild
Cough	Dry severe or hacking	$\pm$
Throat	Fine	Sore
Nose	Dry and clear	Runny
Head	Achy	Headache-free
Appetite	Decreased	Normal
Muscles	Achy	Fine
Chills	Yes	No



#### Zinc for the Treatment of the Common Cold: A Systemic Review and Meta-Analysis of Randomized Controlled Trials

CMAJ 2012;184:E551-561

**Study:** Meta-analysis of 17 randomized control trials with a total of 2121 participants.

**Patients:** All populations.

**Intervention:** Orally administered zinc vs. placebo or no treatment.

**Results:** Patients receiving zinc had a shorter duration of cold symptoms compared with those given placebo (mean difference -1.65 d). Zinc shortened the duration of symptoms in adults but no significant difference was seen in children. Adverse event such as nausea were more common in the zinc group (RR 1.640).

## Common Cold (Acute Rhinitis)



### Definition

- viral URTI with inflammation

### Epidemiology

- most common diagnosis in family medicine, peaks in winter months
- incidence: adults = 2-4/yr, children = 6-10/yr
- organisms
  - mainly rhinoviruses (30-35% of all colds)
  - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
- incubation: 1-5 d
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

### Risk Factors

- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

### Clinical Features

- symptoms
  - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
  - general: malaise, headache, myalgias, mild fever
- signs
  - boggy and erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam
- complications
  - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
  - asthma/COPD exacerbation

### Differential Diagnosis

- allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

## Management

- patient education
  - symptoms peak at 1-3 d and usually subside within 1 wk
  - cough may persist for days to weeks after other symptoms disappear
  - no antibiotics indicated because of viral etiology
  - secondary bacterial infection can present within 3-10 d after onset of cold symptoms
- prevention
  - frequent hand washing, avoidance of hand to mucus membrane contact, use of surface disinfectant
- symptomatic relief
  - rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
  - analgesics and antipyretics: acetaminophen, ASA (not in children because risk of Reye's syndrome)
  - cough suppression: dextromethorphan or codeine if necessary (children under 6 yr of age should not use any cough/cold medications)
  - decongestants, antihistamines
  - zinc lozenge use may help to reduced the duration of cold symptoms
- patients with reactive airway disease will require increased use of bronchodilators and inhaled steroids



### Echinacea for Preventing and Treating the Common Cold

*Cochrane DB Syst Rev* 2006;1:CD000530

This systematic review of 16 trials assessed the effect of Echinacea in preventing and treating common colds. Trials compared preparations containing Echinacea with placebo, no treatment, or an alternative common cold treatment. Variations in preparations and quality of Echinacea made meta-analysis difficult, but in general, results suggested some preparations of Echinacea may be better than placebo.

**Conclusions:** Echinacea preparations vary widely. Some preparations with *E. purpurea* may be effective but results are inconsistent.

## Contraception

- see [Gynecology](#), GY19



**Table 15. Methods of Contraception**

	Advantages	Disadvantages
<b>Combined OCP</b> (e.g. Alesse®, Tri-Cyclen®)	99.9% effective with perfect use, 97-99% with typical use, cycle control, ↓ dysmenorrhea, ↓ menstrual flow, ↓ ovarian cancer, ↓ endometrial cancer, ↓ risk of fibroids, ↓ acne, ↓ hirsutism	Irregular bleeding, systemic hormonal side effects (breast tenderness, nausea, mood changes), no STI protection, slightly increased risk of venous thromboembolism (VTE), MI, stroke, decreased quantity of breast milk postpartum
<b>Progestin Only Pill</b> (e.g. Micronor®)	At least 95% effective with perfect use, no increased risk of VTE, MI or stroke, suitable for postpartum	Hormonal side effects (see Combined OCP) Irregular bleeding, no STI protection, contraceptive reliability requires taking pill at the same time each day (within 3 h), no pill free interval
<b>Transdermal Patch</b> (e.g. Evra®)	Same as OCP, easy to use, changed weekly, 99% effective with correct use	Same as OCP, skin irritation
<b>NuvaRing®</b> (inserted by patient)	Same as OCP, easy to use (in for 3 wk, out for 1 wk), less systemic hormonal side effects, 99% effective with correct use	Same as OCP, vaginitis, some women may be uncomfortable with self-insertion
<b>DMPA</b> IM progesterone injection q12wk (e.g. DepoProvera®)	99.7% effective against pregnancy, infrequent dosing, ↓ menstrual flow or amenorrhea, ↓ risk of endometrial cancer	Irregular bleeding, delayed return of fertility, no STI protection, systemic hormonal side effects (most common is headache), weight gain, ↓ bone mineral density (check after 5 yr)
<b>Male Condom</b>	97% effective against pregnancy and STIs when used properly. When used properly WITH spermicide they are close to 99.9% effective, no Rx required	Latex allergy, irritation, only effective before the expiry date, must be applied properly, can only be used once
<b>Diaphragm</b>	92-96% effective with perfect use, non-hormonal, female-controlled method of contraception, ↓ risk of cervical cancer	Must be left in for 6 h after intercourse, must be used with spermicide, incomplete STI protection, latex allergy, must be fitted by health care worker, ↑ risk of UTI, risk of toxic shock syndrome
<b>Sponge</b>	One-size-fits-all barrier method, does not require fitting by MD, available in pharmacies, 90% effective without a condom, 98% effective with a condom	Relatively expensive, only ~60% effective in parous women, incomplete STI protection, risk of toxic shock syndrome
<b>Intrauterine Device (IUD)</b>	99% effective against pregnancy, effective for 5 yr, no daily regimen required, can be easily removed, ideal in post-partum women	No STI protection, ↑ relative risk of PID in first month, must be inserted by MD, risk of post-insertion vaso-vagal response, risk of uterine rupture is 0.6-1.6 per 1000, 2-10% expulsion rate
Levonorgestrel (e.g. Mirena®) Copper IUD (e.g. Nova T®)	Spotting, less systemic hormonal side effects than OCP  ↓ risk of endometrial cancer, less expensive than Mirena® (~\$170)	Hormonal side effects are possible, but less than OCP (see combined OCP), expensive (~\$400) Irregular bleeding or ↑ menstrual flow, 6-20% women discontinue use in first 5 yr because of pain or ↑ bleeding
<b>Fertility Awareness/Natural Family Planning</b> (e.g. symptothermal method)	Effectiveness: 95-98% with perfect use, 75-88% with typical use, increased awareness of gynecological health, reasonable for couples for whom an unplanned pregnancy would be acceptable	High probability of failure if not used consistently and correctly, no STI protection
<b>Lactational Amenorrhea</b>	Can be effective in breastfeeding women if menses not returned, fully or nearly fully breastfeeding baby and baby is under 6 mo old	Not effective if infant receives any food supplementary to breastfeeding Must breastfeed regularly, even through the night (at least q6h) Most effective is breastfeeding q2-3h



## EMERGENCY CONTRACEPTION (EC)

- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 h apart) or post-coital IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
- post-coital IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
- pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
- advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
- pharmacists across Canada can dispense Plan B® OTC



### Absolute Contraindications to Estrogen Containing Contraception (Combined OCP/Transdermal Patch/Nuvaring)

- Known/suspected pregnancy
- Undiagnosed abnormal vaginal bleeding
- Thromboembolic disorders (e.g. previous DVT, PE)
- Cerebrovascular or coronary artery disease
- Estrogen dependent tumours (breast, uterus)
- Impaired liver function with acute liver disease
- Congenital hypertriglyceridemia
- Smoker age >35
- Migraines with focal neurological symptoms
- Uncontrolled hypertension



### Differential Diagnosis

#### Common Causes

- Upper airway cough syndrome (postnasal drip)
- Asthma/COPD
- GERD
- Non-asthmatic eosinophilic bronchitis

#### Other Causes

- ACE inhibitors
- Aspiration
- Bronchiectasis
- Cystic fibrosis
- Chronic interstitial lung disease
- CHF
- Lung/laryngeal cancer
- Pertussis
- Psychogenic
- Restrictive lung disease
- TB, atypical mycobacterium, and other chronic lung infections



### Dementia Quick Screen

- 3 simple tests, takes about 2 min
- Use when suspect mild cognitive impairment or when patient is at high risk
- Screen involves:
  1. 3 word recall (normal = recalls 2-3 words)
  2. Naming animals in 1 min (normal = >12 in one min)
  3. Clock Drawing – including numbers and hands so time shows 10 min past 11 (normal = correct number/hand placing, or only minor spacing problems)

**INTERPRETATION:** If all 3 results within normal range, cognitive impairment unlikely.

If any results abnormal, possible cognitive impairment, further evaluation necessary.



### Must Ask About/Rule Out

- Bipolar/manic/hypomanic episodes
- Psychosis
- Anxiety
- Bereavement
- Substance use/abuse/withdrawal
- Suicidal/homicidal ideation
- Organic cause

## Cough

### History and Physical

- duration (chronic >3 mo), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptysis, wheezing, chest pain, orthopnea, PND, rhinitis
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (e.g. ACE inhibitors), allergies
- PMH: lung (asthma, COPD, CF), heart (CHF, MI, arrhythmias), chronic illness, GI (reflux)
- vitals including O<sub>2</sub> saturation, respiratory exam, HEENT and precordial exam

### Investigations

- guided by findings on history and physical
  - consider throat swab, CXR, PFTs, upper GI series, sputum culture test for acid-fast bacilli (if TB is suspected)

## Dementia

- see [Psychiatry](#), PS20

### Epidemiology

- 10% in patients over the age of 65, 25% in patients over the age of 85, 50% in patients over the age of 90
- prevalence increases with age, Down syndrome and head trauma
- differential diagnosis: Alzheimer's dementia, vascular dementia, Lewy-Body dementia, frontotemporal dementia

### Investigations

- history, physical, MMSE, MOCA (best screening test), dementia quick screen (see sidebar)
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin B<sub>12</sub>, folate, VDRL, HIV, single photon emission computed tomography, head CT, EEG

### Management

- treat and prevent reversible causes
- provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
- family education, counselling and support (respite programs, group homes)
- pharmacologic therapy: NMDA receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose neuroleptics and antidepressants can be used to treat behavioral and emotional symptoms
- 20% of patients develop clinical depression, most commonly seen in vascular dementia

## Depression

- see [Psychiatry](#), PS9

### Etiology

- often presents as non-specific complaints (e.g. sleep disturbance, chronic fatigue, pain)
- depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of depressed persons may not receive appropriate treatment for their depression
- identification and early treatment improve outcomes



## Screening Questions

- Are you depressed? (high specificity and sensitivity)
- Have you lost interest or pleasure in the things you usually like to do? (anhedonia)
- Do you have problems sleeping?
- For geriatric population, use the Geriatric Depression Scale (GDS) short form for screening

## Assessment

- risk factors: see [Psychiatry](#), PS11
- personal or family history of depression
- medications and potential substance abuse problems
- high risk suicidality/homicidality
  - fill out Form 1 (in Ontario): application by physician to hospitalize a patient against his/her will for psychiatric assessment (up to 72 h)
- functional impairment (e.g. work, relationships)
- at least 5 out of 9 criteria including anhedonia or depressed mood  $\geq 2$  wk for actual diagnosis to be met (see sidebar)
- validated depression rating scales: Beck's depression inventory, Zung's self-rating depression scale, Children's depression inventory, Geriatric Depression Scale, Personal Health Questionnaire Depression Scale (PHQ-9)
- routine medical workup (physical examination, CBC, TSH, electrolytes, urinalysis, glucose, etc.)

## Treatment

- goal: full remission of symptoms and return to baseline psychosocial function
- phases of treatment
  - acute phase (8-12 wk): relieve symptoms and improve quality of life
  - maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
- treatment can consist of pharmacotherapy alone or psychotherapy alone
- combination of antidepressant drug therapy and psychotherapy results in synergistic effects

**Table 16. Common Medications**

Class	Examples	Action	Side Effects	Notes
<b>SSRI</b>	paroxetine (Paxil®) fluoxetine (Prozac®) sertraline (Zoloft®) citalopram (Celexa®) fluvoxamine (Luvox®) escitalopram (Cipralex®)	Block serotonin reuptake	Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase QT interval (baseline ECG is suggested)	First line therapy for teens is fluoxetine; paroxetine is not recommended for teens (controversial)
<b>SNRI</b>	venlafaxine (Effexor®) duloxetine (Cymbalta®)	Block serotonin and NE reuptake	Insomnia, tremors, tachycardia, sweating	
<b>SDRI</b>	bupropion (Wellbutrin®)	Block dopamine and NE reuptake	Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs	Often chosen for lack of sexual side effects, can be used for augmentation of anti-depressant effects with other classes of medication
<b>TCA</b>	amitriptyline (Elavil®)	Block serotonin and NE reuptake	Sexual dysfunction, weight gain, tremors, tachycardia, sweating	Narrow therapeutic window, lethal in overdose

## Prognosis

- up to 40% resolve spontaneously within 6-12 mo
- risks of recurrence: 50% after 1 episode; 70% after 2 episodes; 90% after 3 episodes

# Diabetes Mellitus (DM)

- see [Endocrinology](#), E6

## Epidemiology

- major health concern, affecting up to 10% of Canadians
- type 1 diabetes mellitus (DM1): 10-15% of DM, peak incidence age 10-15
- type 2 diabetes mellitus (DM2): 85-90% of DM, peak incidence age 50-55, up to 60,000 new cases in Canada per year
- gestational diabetes mellitus (GDM): 2-4% of all pregnancies
- incidence of type DM2 is rising dramatically as a result of an aging population, rising rates of obesity, and sedentary lifestyles
- leading cause of new-onset blindness and renal dysfunction
- Canadian adults with diabetes are twice as likely to die prematurely, compared to persons without diabetes



## Differential Diagnosis

- Other psychiatric disorders (e.g. anxiety, personality, bipolar, schizoaffective, seasonal affective disorder, substance abuse/withdrawal)
- Early dementia
- Endocrine (e.g. hyper/hypothyroidism, DM)
- Liver failure, renal failure
- Chronic fatigue syndrome
- Vitamin deficiency (pernicious anemia, pellagra)
- Medication side effects ( $\beta$ -blockers, benzodiazepines)
- Infections (mononucleosis)
- Menopause
- Cancer (50% of patients with tumours, especially of brain, lung and pancreas, develop symptoms of depression before the diagnosis of cancer is made)



## Criteria for Depression

### M-SIGECAPS

- M** Depressed Mood
- S** Increased/decreased Sleep
- I** Decreased Interest
- G** Guilt
- E** Decreased Energy
- C** Decreased Concentration
- A** Increased/decreased Appetite and weight
- P** Psychomotor agitation/retardation
- S** Suicidal ideation

## Common Antidepressants and Dosing

Drug	Starting Dose	Maximum Dose
citalopram (Celexa®)	10-20 mg PO OD	40 mg PO OD
escitalopram (Cipralex®)	5-10 mg PO OD	20 mg PO OD
fluoxetine (Prozac®)	20 mg PO qam	80 mg PO OD
paroxetine (Paxil®)	20 mg PO qam	50 mg PO OD
sertraline (Zoloft®)	25-50 mg PO OD	200 mg PO OD
fluvoxamine (Luvox®)	50 mg PO qhs	300 mg PO OD
venlafaxine (Effexor®)	37.5 mg PO OD	375 mg PO OD
(Effexor XR®)	37.5 mg PO OD	225 mg PO OD
bupropion (Wellbutrin®-immed)	100 mg PO bid	450 mg PO OD
(Sustained release)	100 mg PO qam	400 mg PO OD
amitriptyline (Elavil®)	25 mg PO qhs	300 mg PO OD
mirtazapine (Remeron®)	15 mg PO qhs	45 mg PO OD



## Combined Pharmacotherapy and Psychological Treatment for Depression: A Systematic Review

*Arch Gen Psychiatry* 2004;61:714-719  
**Study:** Systematic review of randomized clinical trials.

**Patients:** 16 trials comprising 1842 patients.

**Intervention:** Antidepressant treatment alone vs. combination of psychological intervention and antidepressant therapy.

**Main outcomes:** Efficacy of and adherence to therapy.

**Results:** Overall, combined therapy was significantly more effective than antidepressant therapy alone (OR 1.86; 95% CI 1.38-2.52), however there was no difference in the rate of dropouts and non-responders in either treatment arm. In studies lasting  $> 12$  wk, combined therapy showed a reduction in dropouts compared to non-responders (OR 0.59; 95% CI 0.39-0.88).

## Risk Factors

- DM1
  - personal or family history of autoimmune disease
- DM2
  - first degree relative with DM
  - age  $\geq 40$  yr
  - obesity (especially abdominal), hypertension, hyperlipidemia, coronary artery disease, vascular disease
  - prior GDM, macrosomic baby ( $>4$  kg)
  - PCOS
  - history of impaired glucose tolerance or impaired fasting glucose
  - presence of complications associated with diabetes
  - presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  - medications: glucocorticoids, atypical antipsychotics, HAART
- both
  - member of a high risk population (e.g. Aboriginal, Hispanic, Asian or African descent)

## Diagnosis

- persistent hyperglycemia is the hallmark of all forms of diabetes

**Table 17. Diagnosis of Insulin Associated Disorders**

Condition	Diagnostic Criteria
DM	One of the following on 2 occasions: <ul style="list-style-type: none"> <li>• Random BG <math>\geq 11.1</math> mmol/L (200 mg/dL) with symptoms of DM (fatigue, polyuria, polydipsia, unexplained weight loss) OR</li> <li>• Fasting BG <math>\geq 7.0</math> mmol/L (126 mg/dL) OR BG 2 h post 75 g OGTT <math>\geq 11.1</math> mmol/L (200 mg/dL) OR HbA1c <math>\geq 6.5\%</math> (in adults)</li> </ul>
Impaired Fasting Glucose (IFG)	Fasting BG = 6.1-6.9 mmol/L (110-124 mg/dL)
Impaired Glucose Tolerance (IGT)	BG 2 h post 75 g OGTT = 7.8-11.0 mmol/L (141-198 mg/dL)

## Screening

- DM2
  - FBG in everyone  $\geq 40$  q3yr, or at high risk using the CANRISK calculator
  - more frequent and/or earlier testing if presence of  $\geq 1$  risk factor (see above)
- GDM (see [Obstetrics](#), OB14)
  - all pregnant women between 24-28 wk gestation
  - non-fasting 1 h 50 g OGCT  $\geq 10.3$  mmol/L (186 mg/dL) is diagnostic
  - if between 7.8-10.2 mmol/L (141-184 mg/dL), do confirmatory fasting 2 h 75 g OGTT
  - if develop GDM, have a 50% chance of developing DM2 over 20 yr

## Goals of Therapy

**Table 18. Goals of Therapy in DM**

General	Avoid complications (e.g. ketoacidosis, hyperglycemia, infection) Prevent long-term complications (microvascular and macrovascular) Minimize negative sequelae associated with therapies (e.g. hypoglycemia, weight gain)
Fasting or Preprandial BG	Ideal: 4-7 mmol/L (72-126 mg/dL) Suboptimal: 7.1-10 mmol/L (128-180 mg/dL); action may be required Inadequate: $> 10.0$ mmol/L (180 mg/dL); action required
HbA1c	$\leq 7\%$ or $\leq 6.5\%$ in some DM2 patients at risk for nephropathy Suboptimal: 7-8.4% Inadequate: $> 8.4\%$
2 h Postprandial BG	5-10 mmol/L (90-180 mg/dL) if HbA1c target met 5-8 mmol/L (90-144 mg/dL) if HbA1c target not met
Blood Pressure	$< 130/80$ in adults (DM and HTN guidelines)
Lipids	LDL $< 2.0$ mmol/L (36 mg/dL) Triglycerides $< 1.5$ mmol/L (27 mg/dL) Total cholesterol/HDL ratio $< 4.0$ mmol/L (72 mg/dL)



### DM Related Symptoms

**Hyperglycemia:** polyphagia, polydipsia, polyuria, weight change, blurry vision, yeast infections.

**Diabetic ketoacidosis (DKA):** fruity breath, anorexia, N/V, fatigue, abdo pain, Kussmaul breathing, dehydration.

**Hypoglycemia:** hunger, anxiety, tremors, palpitations, sweating, headache, fatigue, confusion, seizures, coma.



DKA can be triggered by infection, ischemia, infarction, intoxication, medication non-compliance.



### Long Term Complications of DM

- Microvascular: nephropathy, retinopathy, neuropathy
- Macrovascular: CAD, CVD, PVD



### Screening for Microvascular Complications:

- **Nephropathy:**
  - Urine ACR, serum Cr – Type 2: at diagnosis, then annually;
  - Type 1: 5 yr after diagnosis, then annually)
- **Retinopathy:**
  - Ophthalmology consult – Type 2: at diagnosis then ophtho follow-up q1-2yr; Type 1: 5 yr after diagnosis, then annual follow-up

## Assessment and Monitoring

**Table 19. Assessment and Monitoring**

	Initial Assessment	q2-4months	Annually
<b>History</b>	<ul style="list-style-type: none"> <li>Symptoms of hyperglycemia, ketoacidosis, hypoglycemia</li> <li>Past medical history</li> <li>Functional inquiry</li> <li>Family history</li> <li>Risk factors</li> <li>Medications</li> <li>Sexual function</li> <li>Lifestyle</li> </ul>	<ul style="list-style-type: none"> <li>Diabetes-directed history</li> <li>Screen for awareness and frequency of hypoglycemia and DKA</li> <li>Glucose monitoring</li> <li>Use of insulin and oral agents</li> </ul>	<ul style="list-style-type: none"> <li>Diabetes-directed history</li> <li>Screen for awareness and frequency of hypoglycemia and DKA</li> <li>Glucose monitoring</li> <li>Use of insulin and oral agents</li> <li>Sexual function</li> <li>Lifestyle counselling</li> <li>Psychosocial issues</li> </ul>
<b>Physical</b>	<ul style="list-style-type: none"> <li>General: Ht, Wt, BMI, BP, WC</li> <li>Head and neck: funduscopy, thyroid exam</li> <li>Cardiovascular exam: signs of PVD, pulses, bruits</li> <li>Abdominal exam (e.g. for organomegaly)</li> <li>Hand/foot/skin exam</li> <li>Neurological exam</li> </ul>	<ul style="list-style-type: none"> <li>Wt, BP, BMI, WC</li> <li>Foot exam for sensation (using a 10 g monofilament), ulcers, or infection</li> </ul>	<ul style="list-style-type: none"> <li>Complete neuro exam for peripheral neuropathy</li> <li>Remainder of exam as per PHE</li> </ul>
<b>Investigations</b>	<ul style="list-style-type: none"> <li>FBG, HbA1c, fasting lipids, microalbumin:creatinine ratio</li> <li>ECG</li> </ul>	<ul style="list-style-type: none"> <li>HbA1c q3mo</li> <li>FBG as needed</li> </ul>	<ul style="list-style-type: none"> <li>Fasting lipid profile</li> <li>Resting or exercise ECG if age &gt;35</li> <li>Dipstick analysis for gross proteinuria; if negative: annual microalbuminuria screening with random albumin:creatinine ratio for DM2 and DM1 (5 yr post puberty) If positive: 24-h urine for endogenous creatinine clearance rate and microalbuminuria q6-12mo</li> </ul>
<b>Management</b>	<ul style="list-style-type: none"> <li>Nutritional and physical education</li> <li>Consider referral to diabetes education program if available</li> <li>Monitoring BG: explain methods and frequency</li> <li>Medication counselling: oral hypoglycemics and/or insulin, method of administration, dosage adjustments</li> <li>Pneumococcal vaccination</li> <li>Ophthalmology consult               <ul style="list-style-type: none"> <li>DM1 within 5 yr</li> <li>DM2 at diagnosis</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Assess progress towards long-term complications</li> <li>Adjust treatment plan if necessary</li> </ul>	<ul style="list-style-type: none"> <li>Calibrate home glucose monitor</li> <li>Arrange ophthalmology follow-up annually for DM1 and q2yr for DM2</li> <li>Influenza vaccination annually</li> </ul>

## Nonpharmacologic Management

- diet
  - all diabetics should see a registered dietician
  - can reduce HbA1c by 1-2%
  - strive to attain healthy body weight
  - decrease combined saturated fats and trans-fatty acids to <10% of calories
  - avoid simple sugars, encourage complex carbohydrates, choose low glycemic-index foods
- physical activity and exercise
  - at least 150 min of aerobic exercise per wk, plus 2 sessions per wk of resistance exercise is recommended
  - encourage 30-45 min of moderate exercise 4-7 d/wk
  - promote cardiovascular fitness: increases insulin sensitivity, lowers BP and improves lipid profile
  - if insulin treated, may require alterations of diet, insulin regimen, injection sites and self-monitoring

## Self-Monitoring of Blood Glucose

- DM1: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
- DM2: at least once per day, if once daily insulin regime
- if FBG >14 mmol/L, perform ketone testing to rule out DKA
- if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia



### Long-Term Non-Pharmacological Weight Loss Interventions for Adults with Prediabetes

*Cochrane DB Syst Rev 2005;2:CD005270*

A meta-analysis, using 9 studies comprising 5168 patients, investigated the effectiveness of diet control, physical activity, behavioural weight programs and weight control interventions in adults with pre-diabetes. The analysis was limited by heterogeneous patient populations, but when compared with usual care, weight loss was 2.8 kg and BMI decrease was 1.3 kg/m<sup>2</sup> at 1 yr. Modest but non-significant improvements in glycemic control, BP and blood lipid concentrations were noted. Studies with a follow-up of 3-6 yr showed a significant decrease in diabetes onset when compared with controls.



### Dietary Advice for Treatment of Type 2 DM in Adults

*Cochrane DB Syst Rev 2007;3:CD004097*

A meta-analysis, using 36 articles reporting a total of 18 trials following 1467 participants, showed that there is no high quality data on the efficacy of dietary treatment of type 2 DM. After 6 and 12 mo, adoption of exercise improved HbA1c.

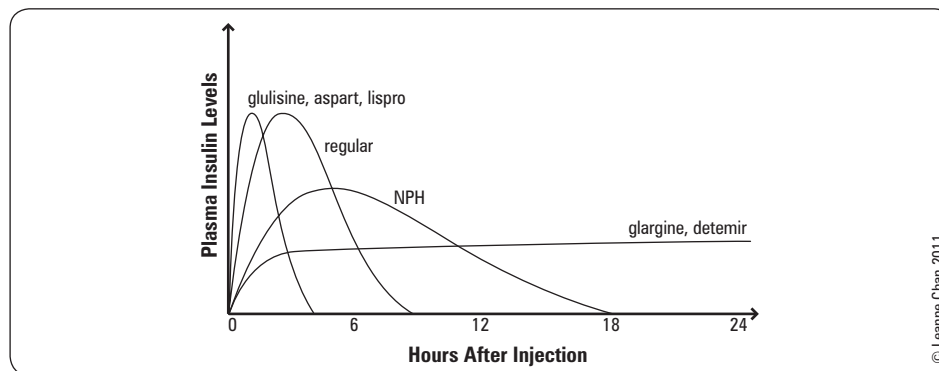


Figure 9. Types of insulin preparation

**Calculate Total Insulin Required:**

DM1: 0.5-0.7 units/kg/d

DM2: 0.3 units/kg/d

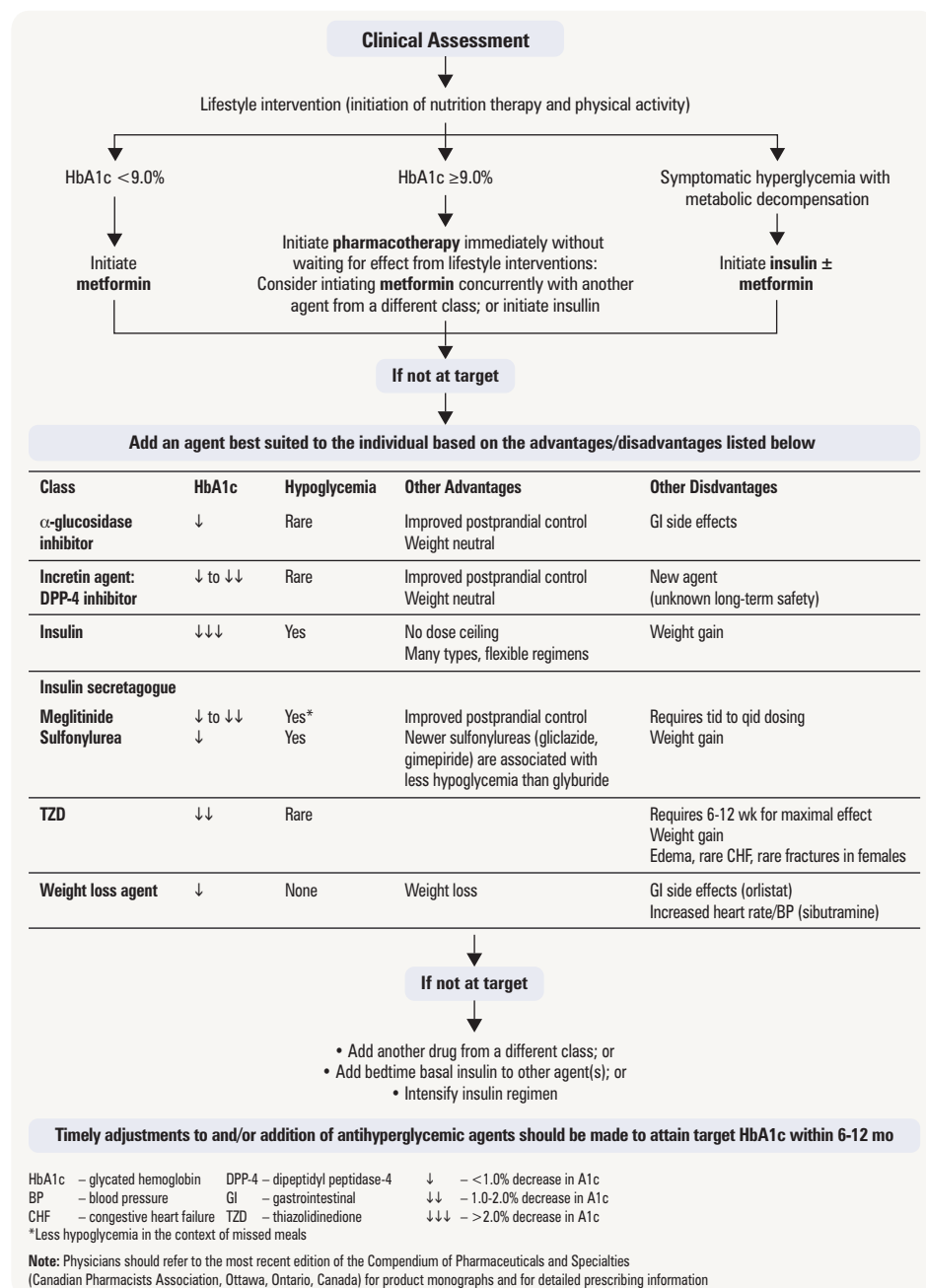


Figure 10. Management of hyperglycemia in type 2 diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic Management of Type 2 Diabetes. Can J Diabetes. 2013;37:S61-S68 (used with permission)

## Hypoglycemic Agents (DM2)

- oral
  - biguanide: metformin (Glucophage®)
  - thiazolidinedione: troglitazone (Rezulin®), rosiglitazone (Avandia®)
  - $\alpha$ -glucosidase inhibitor: acarbose (Precose®)
  - nonsulfonylureas: nateglinide (Starlix®), repaglinide (Gluconorm®)
  - sulfonylureas: glyburide (DiaBeta®), glimepiride (Amaryl®), gliclazide (Diamicon®)
  - DPP-4 inhibitor: sitagliptin (Januvia®)
- injectable
  - GLP-1 analogue: liraglutide (Victoza®)

## Other Medications Used in DM

- ACE inhibitors for:
  - all hypertensive diabetics
  - elevated microalbuminuria (30-300 mg albumin in urine in 24 h)
  - overt nephropathy (>300 mg albumin in urine in 24 h)
  - ARBs are second line for these conditions
- ASA 81 mg once a day for:
  - all diabetics, unless contraindicated
- statins
  - as required to attain target lipid profile



### Canadian Diabetes Association 2008 Clinical Practice Guidelines for Rosiglitazone Use in Type 2 Diabetes:

- 2nd line therapy, 6-12 wk required to achieve full glycemic effect
- Longer duration of glycemic control with monotherapy compared to metformin or glyburide
- Contraindicated in patients with heart failure or LV dysfunction on echo
- Cannot be combined with insulin therapy (increased rates of heart failure)
- Side effects: weight gain (waist to hip ratio not increased), may induce edema and/or congestive heart failure, fractures, rare: macular edema



### Metformin Monotherapy for Type 2 Diabetes Mellitus

*Cochrane DB Syst Rev* 2005;3:CD002966

A Cochrane Review of 29 trials with 37 arms (5259 participants) compared metformin with sulfonylureas, placebo, diet, thiazolidinediones, insulin, meglitinides, and glucosidase inhibitors. The authors concluded that metformin may prevent some vascular complications and mortality in overweight and obese DM2 patients and as such may be considered first line therapy. There is no evidence that the studied alternative therapies have more benefit for glycemia control, body weight, or lipids than does metformin.



### Rosiglitazone Revisited: An Updated Meta-Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality

*Arch Intern Med* 2010;170:1191-1201

Eleven years after the introduction of rosiglitazone, the totality of randomized clinical trials continue to demonstrate increased risk for MI although not for CV or all-cause mortality. The current findings suggest an unfavorable benefit to risk ratio for rosiglitazone.



## Diarrhea

- see [Gastroenterology](#), G15

### Definition

- passage of 3 or more loose or liquid stools in a day or more frequently than is normal for the individual (WHO definition)
- can be acute (<14 d duration) or chronic (>14 d duration)

### Etiology and Clinical Features

- acute diarrhea:
  - majority of cases are self-limiting
  - most commonly caused by viral infection (e.g. rotavirus, norovirus)
  - fever and bloody stools increase probability of bacterial infection
  - consider *C. difficile* infection if recent hospitalization, recent antibiotic use (e.g. broad spectrum antibiotics, fluoroquinolones, clindamycin), chronic use of PPIs, age >65, immunosuppression
- chronic diarrhea:
  - most commonly of non-infectious etiology
  - common causes include drugs (e.g. laxatives, antibiotics), infection (e.g. bacteria, parasites), inflammation (e.g. IBD, diverticulitis), neoplasia (e.g. colon cancer), malabsorption (e.g. celiac disease), maldigestion (e.g. lactose intolerance), and idiopathic

### Treatment

- acute diarrhea: ensure adequate hydration, treat underlying cause (e.g. antibiotics for bacterial infection)
- chronic diarrhea: nonspecific treatment often required before workup is complete
  - oral rehydration solution (if needed): offset electrolyte imbalances
  - lifestyle modification (dietary changes, exercise)
  - fibre (e.g. psyllium): commonly used as adjunctive treatment
  - antidiarrheal opiates (e.g. loperamide): most effective nonspecific treatment
    - ♦ should be used on a scheduled basis before meals rather than prn

## Dizziness

- see [Otolaryngology](#), OT5

### Epidemiology

- 70% see general practitioners initially; 4% referred to specialists
- frequency proportional to age; commonest complaint of ambulatory patients age >75

## Differential Diagnosis

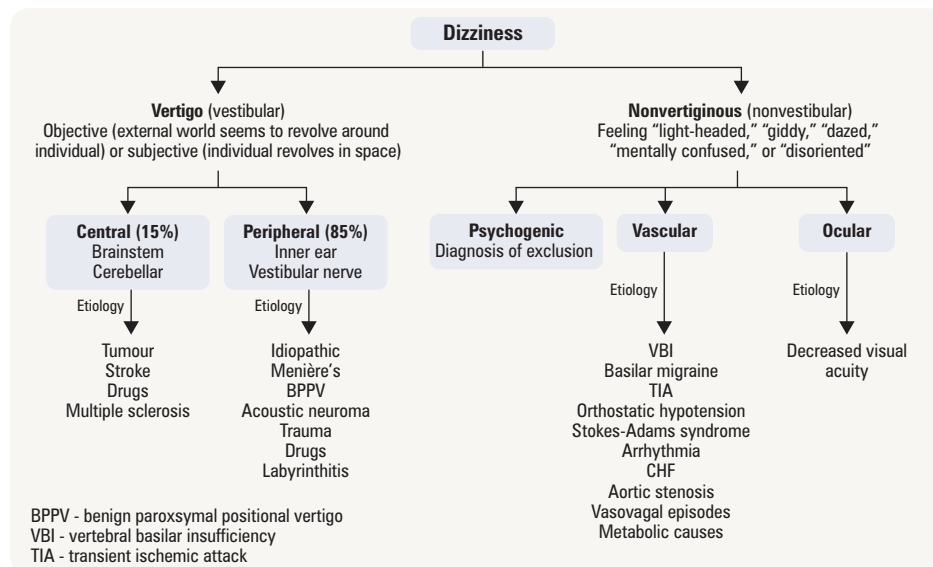


Figure 11. Differential diagnosis of dizziness

### History

- clarify type of dizziness: vertigo, pre-syncope, disequilibrium, light-headedness
- onset, precipitating/alleviating factors, preceding infections and activities, associated symptoms, previous experiences of dizziness
- duration (seconds, minutes, hours, days, weeks, or persistent)
- exacerbations
  - worse with head movement or eye closure (vestibular)
  - no change with head movement and eye closure (nonvestibular)
  - worse with exercise (cardiac/pulmonary causes)
- associated symptoms
  - neurologic (central)
    - transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
    - persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)
  - audiologic (peripheral)
    - hearing loss, tinnitus, otalgia, aural fullness
  - others
    - nausea, vomiting (peripheral vestibular disorders)
    - SOB, palpitations (hyperventilation, cardiac problem)
- general medical history
  - HTN, diabetes, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
  - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - hypotension (secondary to diuresis): furosemide, caffeine, alcohol

### Physical Exam/Investigations

- syncopal
  - cardiac (orthostatic changes in vitals), peripheral vascular, and neurologic exams
  - bloodwork, ECG, 24-h Holter, treadmill stress test, loop ECG, tilt table testing, carotid and vertebral doppler, EEG
- vertiginous
  - ENT and neurologic exams
  - Dix-Hallpike (see sidebar), consider audiometry and MRI if indicated
- non-syncopal, non-vertiginous
  - cardiac and neurologic exams
  - 3-min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG

### Treatment

- guided by history, physical and investigations
- include education, lifestyle modification, physical maneuvers (e.g. Epley for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy and surgery
- refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or if atypical presentation



#### DDx of Vertigo

	BPPV	Labyrinthitis	Menière's	Acoustic Neuroma
Onset	sudden	sudden	gradual	insidious
Duration	seconds	days	min-hours	chronic
Hearing Loss	—	+	+	+
Tinnitus	—	+	+	+
Neuro Sx	—	—	—	+



#### Dix-Hallpike Test

- Have the patient seated with legs extended and head at 45° rotation
- Rapidly shift patient to supine position with head fully supported in slight extension (for 45 s)
- Observe for rotatory nystagmus and ask about sensation of vertigo



## Domestic Violence/Elder Abuse

### INTIMATE PARTNER VIOLENCE

#### Definition

- includes physical, sexual, emotional, psychological and financial abuse (see [Emergency Medicine](#), ER29)

#### Epidemiology

- lifetime prevalence of intimate partner violence against women is between 25-30%
- women who experience abuse have increased rates of injury, death and health consequences including 50-70% increase in gynecological, central nervous system, stress-related problems
- occurs in all socioeconomic, educational and cultural groups with increased incidence in pregnancy, disabled women, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where partner abuse occurs
- physician recognition rates as low as 5%

#### Presentation

- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

#### Management

- screen ALL patients
  - always have a high index of suspicion
  - physician is often first person to get disclosure
  - health care visits are an important opportunity for physicians to address intimate partner violence
  - asking about abuse is the strongest predictor of disclosure
  - several screening tools (see sidebar) exist to identify victims of partner violence
  - make sure to determine the victim's level of immediate and long term danger and ask if there are weapons in the house
- ensure patient safety
  - victim most at risk for homicide when attempting to leave home or following separation
- provide community resources
  - safety planning includes ensuring that there is access to an exit in the home, establishing a safe place to go and having money, clothes, keys, medications, important documents and other emergency items prepared should the patient need to leave quickly
  - shelter or helpline number with legal advocacy and counselling services
  - involve social workers or domestic violence advocates
  - marital counselling inappropriate until safety is established and violence under control
- appointment for follow-up to assess whether condition is better or worse
- reassure patient she/he is not to blame and that the assault is a crime
  - goal is to convey the message that "As your doctor, I am concerned for your safety" and "Your partner has a problem that he/she needs help with" and "I want to help you"
  - reporting suspected or known child abuse is mandatory (see [Emergency Medicine](#), ER59)
  - spousal abuse is a criminal act, but not reportable without the woman's/man's permission
- DOCUMENT all evidence of abuse-related visits for medico-legal purposes (see sidebar)

### ELDER ABUSE

#### Definition

- mistreatment of elderly by those in a position of trust, power, or responsibility for their care
- types of abuse:
  - psychological (e.g. threatening, intimidating, insulting, demeaning, withholding information that may be important to them, ignoring)
  - financial (e.g. stealing, pressuring to sell or share home, misusing power of attorney)
  - physical (e.g. hitting, burning, locking in room, inappropriate use of physical restraints, withholding or misusing medication)
  - sexual
  - neglect

#### Epidemiology

- 7% of adults in Canada age >65 reported experiences of emotional or financial abuse
- older adults who live with someone are more likely to be abused than those who live alone
- 31% of reported violent abuse cases involved family members (Statistics Canada, 2009):
  - most often at the hands of adult children (32%) followed by spouses (28%)
  - older females are more likely to be abused than older males
  - men are more likely than women to be victimized by an adult child (34% vs. 31%)
  - women are more likely than men to experience violence at the hands of a spouse (32% vs. 22%)
- reasons for under-reporting: fear, shame, cognitive impairment, language/cultural barriers, and social and geographic isolation



#### Screening Instruments for Domestic Violence

##### A) Woman Abuse Screening Tool (WAST)-SHORT

- In general how would you describe your relationship?
  - A lot of tension
  - Some tension
  - No tension
- Do you and your partner work out arguments with . . . ?
  - Great difficulty
  - Some difficulty
  - No difficulty

Endorsing either question 1 ("a lot of tension") or question 2 ("great difficulty") makes intimate partner violence exposure likely

##### B) HITS

- How often does your partner:
- Physically hurt you?
  - Insult you?
  - Threaten you with harm?
  - Scream or curse at you?

Each question on HITS to be answered on a 5 point scale ranging from 1 (= never) to 5 (= frequently)  
A total score of 10.5 is significant



#### How to Document Abuse

- Take photographs (with permission) of known or suspected injuries
- Use an injury location chart or "body map" when documenting physical findings
- Document any investigations ordered (e.g. x-ray)
- Write legibly or use a computer
- Record the patient's own words in quotation marks
- Avoid phrases that imply doubt about the patient's reliability (e.g. "patient claims that...")
- Record the patient's demeanor (e.g. upset, agitated)
- Record the time of day the patient is examined and how much time has elapsed since the abuse occurred



#### Risk Factors

- Female
- Older age (age 80 and older)
- Physical and mental frailty

**Screening**

- insufficient evidence to include or exclude as part of the periodic health examination, but recommended that physicians be alert for indicators of abuse and institute measures to prevent further abuse
- general questions such as “Do you feel safe at home?” and move into more specific questions about different kinds of abuse

**Presentation**

- signs that an older adult is being abused may include:
  - depression, fear, anxiety, passivity, unexplained injuries, dehydration, malnutrition, poor hygiene, rashes, pressure sores, and over-sedation/inappropriate medication use

**Management**

- gather information from all sources (e.g. family members, health care providers, neighbours)
- perform a thorough physical examination
- ensure immediate safety and devise a plan for follow-up
- additional steps depend on whether the patient accepts intervention and whether they are capable of making decisions about their care
- interventions may include use of protective and legal services, senior resource nurses, elder abuse intervention teams and senior support groups

## Dyspepsia

- see [Gastroenterology](#), G10

**Definition and Clinical Features**

- defined as epigastric pain or discomfort
- can be associated with fullness, belching, bloating, heartburn, food intolerance, nausea or vomiting

**Epidemiology**

- annual incidence 1-2%, prevalence 20-40%

**Etiology**

- common: functional, peptic ulcer disease, gastroesophageal reflux disease (GERD), gastritis
- others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

**History**

- symptoms may not be useful in finding cause
- association with food, anorexia, nausea, vomiting, NSAID use

**Investigations and Management**

- lifestyle modifications: dietary changes, decreased EtOH consumption, smoking cessation
- empiric therapy: H<sub>2</sub> receptor blockers, proton pump inhibitors (PPIs) for short periods of time (8 wk with taper)
- testing for *H. pylori*: serology, urea breath test
- upper endoscopy (preferred), upper GI series

**Dyspepsia Red Flags**

- Weight loss
- Dysphagia
- Persistent vomiting
- GI bleeding (hematemesis, hematochezia, melena)
- Onset age >50

**DDx of Dyspnea****Pulmonary**

- COPD
- Asthma
- Restrictive lung disease
- Pneumothorax
- Congenital lung disease

**Cardiac**

- CHF
- CAD
- MI (recent or past)
- Cardiomyopathy
- Valve dysfunction
- Pericarditis
- Arrhythmia
- Hypertrophy

**Mixed/Other**

- Deconditioning
- Trauma
- Pain
- Neuromuscular
- Metabolic condition
- Functional: anxiety, panic attack, hyperventilation

## Dyspnea

- see [Respirology](#), R3 and [Emergency Medicine](#), ER27

**History and Physical**

- history
  - cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema
  - asthma, allergy, eczema, ASA/NSAID sensitivity, nasal polyps
  - constitutional symptoms
  - smoking, recreational drugs, medications
  - occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  - travel and birth place
  - FHx of atopy
  - previous CXR or PFTs
- physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

**Investigations**

- CXR, ECG
- PFTs, ABG acutely if indicated

**Management**

- ABCs: send to ER if in severe respiratory distress
- depends on cause

## Dysuria

- see [Urology](#), U5

### Definition

- the sensation of pain, burning or discomfort on urination

### Epidemiology

- in adulthood, more common in women than men
- approximately 25% of women report one episode of acute dysuria per year
- most common in women age 25-54 and in those who are sexually active
- in men, dysuria becomes more prevalent with increasing age

### Etiology

- infectious
  - most common cause
  - presents as cystitis, urethritis, pyelonephritis, vaginitis or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, chemicals, foreign bodies, trauma, neoplasm, kidney stones

**Table 20. Etiology, Signs and Symptoms of Dysuria**

Infection	Etiology	Signs and Symptoms
UTI/Cystitis	KEEPS bacteria ( <i>Klebsiella</i> , <i>E. coli</i> , <i>Enterobacter</i> , <i>Proteus mirabilis</i> , <i>Pseudomonas</i> , <i>S. saprophyticus</i> )	Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)
Urethritis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , <i>Trichomonas</i> , <i>Candida</i> , herpes	Initial dysuria, urethral/vaginal discharge, history of STI
Vaginitis	<i>Candida</i> , <i>Gardnerella</i> , <i>Trichomonas</i> , <i>C. trachomatis</i> , atrophic, herpes, lichen sclerosis	External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding
Prostatitis	<i>E. coli</i> , <i>C. trachomatis</i> , <i>S. saprophyticus</i> , <i>Proteus mirabilis</i> , <i>Enterobacter</i> , <i>Klebsiella</i> , <i>Pseudomonas</i>	Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain
Pyelonephritis	<i>E. coli</i> , <i>S. saprophyticus</i> , <i>Proteus mirabilis</i> , <i>Enterobacter</i> , <i>Klebsiella</i> , <i>Pseudomonas</i>	Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, nausea or vomiting

### Investigations

- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteriuria, hematuria
- urine C&S
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomonas, endocervical/urethral swab or urine PCR for *N. gonorrhoeae* and *C. trachomatis*
- radiologic studies and other diagnostic tests if atypical presentation
- see [Pediatrics](#), P65 for UTI in children

### Management

- see [Antimicrobial Quick Reference](#), FM55 for treatment
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic, due to risk of preterm labour; need to follow with monthly urine cultures and retreat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
- urethritis
  - when swab or PCR is positive for chlamydia or gonorrhea must report to Public Health
  - all patients should return 4-7 d after completion of therapy for clinical evaluation



#### UTI Clinical Decision Aid

- Dysuria
- + Leukocytes
- + Nitrites

if 2 or more criteria MET, then treat without culture, otherwise culture required prior to treatment.

*Arch Intern Med* 2007;67:2201-2206



#### Risk Factors for Complicated UTI

- Male sex
- Pregnancy
- Recent urinary tract instrumentation
- Functional or anatomic abnormality of the urinary tract
- Chronic renal disease
- Diabetes
- Immunosuppression
- Indwelling catheter



#### Prevention of UTIs

- Maintain good hydration (especially with cranberry juice) (recommendation level I)
- Wipe urethra from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse



#### Cranberries for Preventing Urinary Tract Infections

*Cochrane DB Syst Rev* 2008;1:CD001321

**Study:** Meta-analysis of 10 RCTs, n=1049.

**Patients:** All populations.

**Intervention:** Cranberry juice vs. placebo, juice or water was evaluated in seven studies, and cranberry tablets vs. placebo in four studies.

**Main Outcome:** UTIs – symptomatic and asymptomatic.

**Results:** Cranberry products significantly reduced the incidence of UTIs at 12 mo (RR 0.65, 95% CI 0.46 to 0.90) compared with placebo/control.

**Conclusion:** There is some evidence that cranberry products may decrease the number of symptomatic UTIs over a 12 mo period, particularly for women with recurrent UTIs.

## Epistaxis

- see [Otolaryngology](#), OT26



**Table 21. Characteristics of Anterior vs. Posterior Bleeds**

	Anterior (90%)	Posterior (10%)
<b>Location/ Origin</b>	Little's area/Kiesselbach's plexus	Woodruff's plexus/sphenopalatine artery
<b>Age (yr)</b>	2-10, 50-80	Usually >50
<b>Common Cause</b>	Trauma (digital, fracture, foreign body), dry air, cool climate, post URTI, nasal dryness, chemical (nasal sprays, cocaine), tumour	Systemic: hepatic disease, primary/secondary bleeding disorder, medications (ASA, NSAIDs, warfarin), HTN, atherosclerosis
<b>Investigations</b>	Bloodwork (CBC, INR/PTT, cross and type, LFTs) Imaging (x-ray, CT as needed, nasopharyngoscopy)	Same as for anterior bleeds
<b>Treatment</b>	Conservative: <ul style="list-style-type: none"> <li>• Position: upright leaning forward with direct digital pressure over soft part of nostril for &gt;10 min ("pinch" up to cartilage)</li> <li>• Humidifier in bedroom, nasal saline sprays, bacitracin or Vaseline® application to Little's area</li> <li>• Silver nitrate</li> <li>• Gelfoam/hemostat</li> <li>• Nasal packing with Vaseline® gauze, nasal catheter or sponge</li> <li>• Cotton soaked in vasoconstrictor (oxymetazoline 0.5%) and topical anesthetic (4% lidocaine) placed in anterior nasal cavity with direct pressure for &gt;10 min</li> </ul>	Emergency: ENT/ER consult for posterior packing with an intranasal balloon/foley catheter embolization/surgery
<b>Prognosis</b>	Usually stops with >10 min of pressure to nose	Copious bleed, often swallowed and vomited May lead to hypovolemic shock if not treated promptly

## Erectile Dysfunction (ED)

- see [Urology](#), U30

### Definition

- consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance of  $\geq 3$  mo duration

### Epidemiology

- ~20% of men aged 40; ~50% of men aged 70

### Etiology

- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, diabetes), anatomic (structural abnormality, e.g. Peyronie's), neurologic (post-op, diabetes), medications (clonidine, antihypertensives, psychotropics)
- psychogenic (10%)

**Table 22. Differentiation Between Organic and Psychogenic ED**

Characteristic	Organic	Psychogenic
<b>Onset</b>	Gradual	Acute
<b>Circumstances</b>	Global	Situational
<b>Course</b>	Constant	Varying
<b>Non-coital erection</b>	Poor	Rigid
<b>Morning erection</b>	Absent	Present
<b>Psychosexual problem</b>	Secondary	Long history
<b>Partner problem</b>	Secondary	At onset
<b>Anxiety and fear</b>	Secondary	Primary

Walsh: Campbell's Urology, 8th ed. Table 46-4

### History

- comprehensive sexual, medical and psychosocial history
- time course
  - last satisfactory erection
  - gradual or sudden onset
  - attempts at sexual activity



### DDx of Erectile Dysfunction

#### PENIS

Psychogenic  
Endocrine (DM2, testosterone)  
Neurogenic (DM2, post-operative)  
Insufficiency of blood (atherosclerosis)  
Substances

- quantify (see Table 22, FM31)
  - presence of morning or night time erections
  - stiffness (scale of 1-10)
  - ability to initiate and maintain an erection with sexual stimulation
  - erection stiffness during sex (scale of 1-10)
- qualify
  - partner or situation specific
  - loss of erection before penetration or climax
  - degree of concentration required to maintain an erection
  - percentage of sexual attempts satisfactory to patient and/or his partner
  - significant bends in penis or pain with erection
  - difficulty with specific positions
  - impact on quality of life and relationship

### Investigations

- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: fasting glucose, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
  - psychological and/or psychiatric consultation
  - in-depth psychosexual and relationship evaluation
  - nocturnal penile tumescence and rigidity (NPTR) assessment
  - vascular diagnostics (e.g. doppler studies, angiography)

### Management

**Table 23. Management of Erectile Dysfunction**

Nonpharmacologic	Pharmacologic	Surgical
Lifestyle changes (alcohol, smoking, exercise)	Oral agents	Implants
Relationship/sexual counselling	Suppository	Vascular repair
Vacuum devices	Male urethral suppository for erection (MUSE)	Realignment
	Injections	

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors (see Table 24)
  - $\alpha$ -adrenergic blockers (e.g. yohimbine)
  - serotonin antagonist and reuptake inhibitor (e.g. trazodone)
  - testosterone – currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications)

**Table 24. Phosphodiesterase Type 5 Inhibitors**

Examples	Dosing (1 dose/d)	Specifics	Side Effects	Contraindications
sildenafil (Viagra®)	25-100 mg/dose	Take 0.5-4 h prior to intercourse May last 24 h	Flushing, headache, indigestion	Not to be used in patients taking nitrates
tadalafil (Cialis®)	5-20 mg/dose	Effects may last 36 h	As above	As above
vardenafil (Levitra®)	2.5-20 mg/dose	Take 1 h prior to intercourse	As above	As above



#### The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction

*Arch Intern Med* 2011;171:1797-1803

**Study:** Meta-analysis of 6 RCTs.

**Population:** 740 male participants.

**Intervention:** Lifestyle modification and pharmacotherapy targeting CAD risk factors.

**Main outcome measure:** International Index of Erectile Dysfunction (IIEF-5) score.

**Results:** Lifestyle modifications and pharmacotherapy for cardiovascular risk factors had a statistically significant association with improved sexual function (weighted mean difference 2.66; 95% CI 1.86-3.47). Lifestyle modification without use of statins was also statistically significantly associated with improved sexual function (weighted mean difference 2.40; 95% CI 1.19-3.61).

**Conclusion:** Lifestyle modification alone or combined with pharmacotherapy can improve sexual function.

## Eye Complaints

- see [Ophthalmology](#), OP3, for *Vision Loss* and *Red Eye*



## Falls in the Elderly

- see [Geriatric Medicine](#), GM5



## Fatigue

### Epidemiology

- 25% of office visits to family physicians
  - peaks in ages 20-40
  - women 3-4x > men
- 50% have associated psychological complaints/problems, especially if <6 mo duration



#### Fatigue Red Flags

- Fever
- Weight loss
- Night sweats
- Neurological deficits
- Ill-appearing

## Differential Diagnosis

**Table 25. Differential Diagnosis of Fatigue: PS VINDICATE**

<b>P</b>	<b>Psychogenic</b>	<b>Depression, sleep disorder, life stresses</b> , anxiety disorder, chronic fatigue syndrome, fibromyalgia
<b>S</b>	Sedentary	Unhealthy/sedentary lifestyle, <b>obstructive sleep apnea</b>
<b>V</b>	Vascular	Stroke
<b>I</b>	<b>Infectious</b>	Viral (e.g. mononucleosis, hepatitis, HIV), bacterial (e.g. TB), fungal, parasitic
<b>N</b>	<b>Neoplastic</b>	Any malignancy
	Nutrition	<b>Anemia</b> (Fe deficiency, B <sub>12</sub> deficiency)
	Neurogenic	Myasthenia gravis, multiple sclerosis, Parkinson's disease
<b>D</b>	<b>Drugs</b>	β-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics
<b>I</b>	Idiopathic	
<b>C</b>	Chronic illnesses	CHF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease
<b>A</b>	Autoimmune	SLE, RA, mixed connective tissue disease, polymyalgia rheumatica
<b>T</b>	Toxin	<b>Substance abuse</b> (e.g. alcohol), heavy metal
<b>E</b>	Endocrine	<b>Hypothyroidism, diabetes</b> , Cushing's syndrome, adrenal insufficiency, pregnancy

Common causes are in **bold**

## Investigations

- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical examination
- investigations should be guided by history and physical and may include:
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vit B<sub>12</sub>, serum protein electrophoresis, Bence-Jones, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - urinalysis, CXR, ECG
  - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests

## Treatment

- treat underlying cause
- if etiology cannot be identified (1/3 of patients)
  - reassurance and follow-up, especially with fatigue of psychogenic etiology
  - quick followup for reassurance
  - supportive counselling, behavioural, or group therapy
  - encourage patient to stay physically active to maximize function
  - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
  - prognosis: after 1 yr, 40% are no longer fatigued

## CHRONIC FATIGUE SYNDROME (CFS)

**Definition (CDC 2006)** – must meet both criteria

1. new or definite onset of unexplained, clinically evaluated, persistent or relapsing chronic fatigue, not relieved by rest, which results in occupational, educational, social, or personal dysfunction
  2. concurrent presence of at least 4 of the following symptoms for a minimum of 6 mo:
    - impairment of short-term memory or concentration, severe enough to cause significant decline in function
    - sore throat
    - tender cervical or axillary lymph nodes
    - muscle pain
    - multi-joint pain with no swelling or redness
    - new headache
    - unrefreshing sleep
    - post-exertion malaise lasting >24 h
- exclusion criteria: medical conditions that may explain the fatigue, certain psychiatric disorders (depression with psychotic or melancholic features, schizophrenia, eating disorders), substance abuse, severe obesity (BMI >45)

## Epidemiology

- F>>M, Caucasians > other groups, majority in their 30s
- found in <5% of patients presenting with fatigue

## Etiology

- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency



### Exercise Therapy for Chronic Fatigue

Cochrane Depression, Anxiety, and Neurosis Group  
Cochrane DB Syst Rev 2004;Issue 3

**Purpose:** To determine the effectiveness of exercise therapy for Chronic Fatigue Syndrome (CFS).

**Methods:** Systematic review of 5 RCTs with 336 patients of all ages with a clinical diagnosis of CFS.

**Interventions:** Exercise therapy alone was compared with treatment as usual (or relaxation and flexibility), pharmacotherapy (fluoxetine), or exercise therapy combined with either pharmacotherapy or patient education.

**Results:** At 12 wk, patients undergoing exercise therapy were less fatigued than controls (SMD -0.77; 95% CI, -1.26 to -0.28). Physical functioning was also significantly improved, but there were more dropouts with exercise therapy. Compared with fluoxetine, patients receiving exercise therapy were less fatigued (WMD -1.24; 95% CI, -5.31 to 2.83). Patients receiving combination therapy with exercise therapy and either fluoxetine or patient education, did better than those on monotherapy.

**Conclusions:** Patients may benefit from exercise therapy. Combination therapy with either fluoxetine or education may offer additional benefit. Further high quality trials are needed.



## Investigations

- no specific diagnostic laboratory tests

## Treatment

- promote sleep hygiene
- provide support and reassurance that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy (e.g. CBT), family therapy, support groups
- pharmacological
  - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials, antiallergy therapy, antihypertensive therapy

## Fever

- see [Pediatrics](#), P54, for fever in pediatric population

## Definition

- oral temperature  $>37.2^{\circ}\text{C}$  (AM),  $37.7^{\circ}\text{C}$  (PM)
- fever in children under 2 must be a rectal temperature for accuracy
- TM not accurate for measurement until child is over the age of 5

**Table 26. Differential Diagnosis of Fever**

Infection	Cancer	Medications		Other
Bacterial	Leukemia	Allopurinol	Nifedipine	Irritable Bowel Syndrome
Viral	Lymphoma	Captopril	Phenytoin	Collagen-vascular disease
TB	Other Malignancies	Cimetidine	Diuretics	DVT
		Heparin	Barbiturates	
		INH	Antihistamines	
		Meperidine		

## History

- fever
  - peak temperature, thermometer, route, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
- symptoms of possible source
  - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
  - pneumonia: cough, pleuritic chest pain
  - URTI: cough, coryza, ear pain
  - meningitis: headache, confusion, stiff neck, rash
  - osteomyelitis: bone pain
  - skin: purulent discharge
  - PID: discharge, dyspareunia, lower abdominal pain
  - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
  - medications
    - PE/DVT: swollen legs, pain in calf, shortness of breath, pleuritic chest pain
    - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, day care, contact with TB, foodborne, animals

## Investigations

- CBC and differential, blood culture, urine culture, urinalysis
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- LP

## Management

- increase fluid intake
- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause



### Mean Body Temperature

- Oral =  $36.8^{\circ}\text{C}$
- Tympanic Membrane =  $36.4^{\circ}\text{C}$
- Rectal =  $37.2^{\circ}\text{C}$
- Diurnal Variation =  $0.5^{\circ}\text{C}$  higher at 4 pm vs. 6 am
- See [Pediatrics](#), P54 for normal temperature in children

## Joint Pain

- see [Rheumatology](#), RH3



**Table 27. Differential Diagnosis of Joint Pain**

Non-Articular		Articular	
Localized	Generalized	Inflammatory	Degenerative
Bursitis Tendonitis Capsulitis	Fibromyalgia Polymyalgia rheumatica	Seropositive <ul style="list-style-type: none"> <li>• Rheumatoid arthritis</li> <li>• Systemic lupus erythematosus</li> <li>• Scleroderma</li> <li>• Polymyositis</li> <li>• Sjogren's syndrome</li> </ul>	Primary <ul style="list-style-type: none"> <li>• Familial Heberden's node</li> <li>• Osteoarthritis</li> <li>• Regional hip or knee</li> </ul>
		Seronegative <ul style="list-style-type: none"> <li>• Ankylosing spondylitis</li> <li>• Inflammatory bowel disease</li> <li>• Psoriatic arthritis</li> <li>• Reactive arthritis</li> </ul>	Secondary <ul style="list-style-type: none"> <li>• Metabolic</li> <li>• Hemophilic</li> <li>• Neuropathic</li> <li>• Traumatic</li> </ul>
		Crystal <ul style="list-style-type: none"> <li>• Gout</li> <li>• Pseudogout</li> <li>• Milwaukee shoulder, calcific periarthritis</li> </ul>	
		Infectious <ul style="list-style-type: none"> <li>• Gonococcal</li> <li>• Non-gonococcal</li> </ul>	

### History

- number of joints involved: monoarticular, oligoarticular, polyarticular
- pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
- onset: acute vs. chronic (>6 wk)
- trauma, infection, medications (steroids, diuretics)
- FHx of arthritis
- co-morbidities: diabetes mellitus (carpal tunnel syndrome), renal insufficiency (gout), psoriasis (psoriatic arthritis), myeloma (low back pain), osteoporosis (fracture), obesity (OA)
- constitutional symptoms (neoplasm)

### Physical Exam

- vitals
- specific joint exams
- systemic features (skin, nails, eyes, hands)

### Investigations

- CBC and differential, ESR, CRP, RF, ANA, HLA-B27, serum uric acid, calcium
- urinalysis
- tissue cultures
- x-ray
- joint aspirate for cell count + differential, culture, Gram stain, microscopy

### Treatment

- patient education including lifestyle modifications
- physiotherapy, occupational therapy
- manage pain (acetaminophen, NSAIDs)
- treat specific causes (antibiotics, DMARDs)



#### Signs and Symptoms of Inflammatory Arthritis

##### WARM(S) joints

Worse with rest, better with activity  
Awakening in the latter half of the night  
Redness around joint  
Morning stiffness (>30 min)  
Soft tissue swelling, erythema



#### Systemic Features

- Fever (SLE, infection)
- Rash (SLE, psoriatic arthritis)
- Nail abnormalities (psoriatic, reactive arthritis)
- Uveitis (psoriatic, reactive arthritis, ankylosing spondylitis)
- Myalgias (fibromyalgia, myopathy)
- Weakness (polymyositis, neuropathy)
- GI symptoms (scleroderma, IBD)
- GU symptoms (reactive arthritis, gonococemia)

## Headache

- see [Neurology](#), N38

### Primary Headaches

**Table 28. Primary Headaches**

	Migraine	Tension-type	Cluster	Caffeine Withdrawal
<b>Epidemiology</b>	12% of adults F>M 20% with aura 80% without aura	38% of adults, can be episodic or chronic	<0.1% of adults, M>>F	~50% of people drinking >2.5 cups/d
<b>Duration</b>	5-72 h	May occur as isolated incident or daily, duration is variable	<3 h at same time of day	Begins 12-24 h after last caffeine intake, can last ~1 wk
<b>Pain</b>	Classically unilateral and pulsatile, but 40% are bilateral, moderate-severe intensity, nausea/vomiting, photo-/phonophobia	Mild to moderate pain, bilateral, fronto-occipital or generalized pain, band-like pain, ± contracted neck/scalp muscles, associated with little disability	Sudden, unilateral, severe, usually centered around eye, frequently awakens patient Associated conjunctival injection and tearing "Suicide" headache	Severe, throbbing, associated with drowsiness, anxiety, muscle stiffness, nausea, waves of hot or cold sensations
<b>Triggers</b>	Numerous (e.g. food, sleep disturbance, stress, hormonal, fatigue, weather, high altitude) Aggravated by physical activity	Stressful events, NOT aggravated by physical activity	Often alcohol	Discontinuing caffeine
<b>Treatment of Acute Headache</b>	1 <sup>st</sup> line: acetaminophen, ASA ± caffeine 2 <sup>nd</sup> line: NSAIDs 3 <sup>rd</sup> line: 5HT agonists ± antiemetic	Rest and relaxation NSAIDs	Sumatriptan Dihydroergotamine High-flow O <sub>2</sub> Intranasal lidocaine	Caffeine Acetaminophen or ASA ± caffeine
<b>Prophylactic Therapy</b>	1 <sup>st</sup> line: β-blockers 2 <sup>nd</sup> line: TCAs 3 <sup>rd</sup> line: anticonvulsants	Rest and relaxation, physical activity, biofeedback	Lithium carbonate, prednisone, methysergide	Cut down on caffeine

### Secondary Headaches

- caused by underlying organic disease
- account for <10% of all headaches, may be life-threatening
- etiology
  - aneurysm
  - space-occupying lesion
  - systemic infection (meningitis, encephalitis)
  - stroke
  - subarachnoid hemorrhage
  - systemic disorders (thyroid disease, hypertension, pheochromocytoma, etc.)
  - temporal arteritis
  - traumatic head injuries
  - TMJ or C-spine pathology
  - serious ophthalmological and otolaryngological causes of headache
- treatment
  - based on underlying disorder
  - analgesics may provide symptomatic relief

### Investigations

- indicated only when red flags are present and may include:
  - CBC for suspected systemic or intracranial infection
  - ESR for suspected temporal arteritis
  - neuroimaging (CT or MRI) to rule out intracranial pathology
  - CSF analysis for suspected intracranial hemorrhage, infection



#### Headache Red Flags

##### SN00P

Systemic symptoms or illnesses

- fever
- anticoagulation
- pregnancy
- cancer

Neurologic signs/symptoms

- impaired mental status
- neck stiffness
- seizures
- focal neurologic deficits

Onset

- sudden and severe
- new headache after age 50

Other associated conditions

- following head trauma
- awakens patient from sleep
- jaw claudication
- scalp tenderness
- worse with exercise, sexual activity or Valsalva

Prior headache history

- different pattern
- rapidly progressing in severity/frequency



#### Migraine Screen

##### POUND

Pulsatile quality

Over 4-72 h

Unilateral

Nausea and vomiting

Disabling intensity

if ≥4 present then a diagnosis is likely  
(+LR = 24)



#### Acupuncture for Migraine Prophylaxis

Cochrane DB Syst Rev 2009;4:CD001218

Study: Meta-analysis of 22 RCTs.

Population: 4419 participants with diagnosed migraine.

Intervention: Preventative treatment with acupuncture, sham acupuncture, no prophylactic treatment/routine care only, other interventions.

Main outcome measure: Proportion of responders in 3-4 mo. Other outcomes: frequency of migraine attacks, number of migraine days, headache frequency.

Results: Patients receiving acupuncture had higher response rates and fewer headaches after 3-4 mo than those with no prophylactic treatment or routine care only. There was no statistically significant difference between "true" vs. "sham" acupuncture.

Conclusion: Acupuncture is a viable prophylactic treatment option for migraine attacks. Selecting specific points for acupuncture is not as important as believed by practitioners.

## Hearing Impairment

- see [Otolaryngology](#), OT9

### Definition

- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

### Epidemiology

- 10% of the population is hard of hearing or deaf
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people over 65
- associated with significant physical, functional and mental health consequences

### Classification

- conductive (sound does not reach cochlea)
- sensorineural (sound is not converted or transmitted via neural signals)
- mixed

### Assessment

- infants
  - universal newborn hearing screening program
- elderly
  - whispered-voice test
    - ♦ whisper six test words 6 inches to 2 feet away from the patient's ear out of the visual field, ask patient to repeat the words (with non-test ear distraction)
  - tuning fork test
    - ♦ Rinne and Weber (not for general screening)
  - audioscope
    - ♦ delivers pure tone frequencies to obtain thresholds for frequencies of 250-8000 Hz

### Management

- counsel about noise control and hearing protection programs (grade A evidence)
- refer patients with hearing loss for a complete audiological examination
- hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life



#### Does this Patient have Hearing Impairment?

JAMA 2006;295:416-428

**Purpose:** To evaluate bedside clinical maneuvers used to evaluate the presence of hearing impairment.

**Study:** Evidence-based review of studies examining the accuracy or precision of screening questions and tests. 24 studies were included in this analysis.

**Conclusions:** Elderly patients who admit to having hearing impairment should be offered audiometry, while those who do not should undergo a whispered-voice test. Those who hear the whispered voice require no further testing, while those who do not require audiometry. The Weber and Rinne tests are not useful in screening for hearing impairment.

## Hypertension

Hypertension Guidelines are reviewed and updated annually.

For up to date recommendations, please see [www.hypertension.ca/chep](http://www.hypertension.ca/chep)

### Epidemiology

- 20-25% of Canadian adults have HTN (up to 50% undiagnosed)
- 16% of those diagnosed are well controlled
- approximately 50% of adult Canadians are hypertensive by age 60
- 3rd leading risk factor associated with death
  - risk factor for CAD, CHF, cerebrovascular disease, renal failure, peripheral vascular disease

### Definition

- hypertension
  - BP  $\geq 140/90$  mmHg, unless DM ( $\geq 130/80$  mmHg), or age  $\geq 80$  yr ( $\geq 150/90$  mmHg)
- isolated systolic hypertension
  - sBP  $\geq 140$  and dBP  $< 90$
  - associated with progressive reduction in vascular compliance
  - usually begins in 5<sup>th</sup> decade
- accelerated hypertension
  - significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy but without papilledema
- malignant hypertension
  - sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
  - not defined by absolute level of BP, but often requires BP of  $> 200/140$
- hypertensive urgency
  - sBP  $> 210$  or dBP  $> 120$  with minimal or no target-organ damage
- hypertensive emergency
  - high BP + acute target-organ damage



Symptoms of hypertension are usually NOT PRESENT (this is why it is called the "silent killer").

May have occipital headache upon awakening or organ specific complaints if advanced disease.

## Etiology

- essential (primary) hypertension (>90%)
  - undetermined cause
- secondary hypertension (10%), see Table 29
- watch for labile, “white coat” hypertension (office-induced elevated BP)

## Predisposing Factors

- family history
- obesity (especially abdominal)
- alcohol consumption
- stress
- sedentary lifestyle
- smoking
- male gender
- age >30
- excessive salt intake/fatty diet
- African American ancestry
- dyslipidemia

**Table 29. Causes of Secondary Hypertension**

	Common Cause		
<b>Renal</b>	Renovascular HTN Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney		
<b>Endocrine</b>	1° hyperaldosteronism Pheochromocytoma Cushing's syndrome Hyperthyroidism/hyperparathyroidism Hypercalcemia of any cause		
<b>Vascular</b>	Coarctation of the aorta Renal artery stenosis		
<b>Drug-induced</b>	Estrogens MAOIs Cocaine	Steroids Lithium Amphetamines	NSAIDs Decongestants Alcohol

## Investigations

- for all patients with hypertension
  - CBC, electrolytes, Cr, fasting glucose and lipid profile, 12-lead ECG, urinalysis
- for specific patient subgroups
  - DM OR renal disease: urinary protein excretion
  - increasing Cr OR history of renal disease OR proteinuria OR HTN resistant to 3 meds OR presence of abdominal bruit: renal ultrasound, captopril renal scan, MRA/CTA
  - if suspected endocrine cause: plasma aldosterone, plasma renin
  - if suspected pheochromocytoma: 24 h urine for metanephrines and catecholamines
  - ECG for left ventricular dysfunction assessment if indicated



### Hypertensive Emergencies

- Malignant HTN**
- Cerebrovascular:**
  - Hypertensive encephalopathy
  - CVA with severe hypertension
  - Intracerebral hemorrhage
  - SAH
- Cardiac:**
  - Acute aortic dissection
  - Acute refractory LV failure
  - Acute MI with persistent ischemic pain after CABG
- Renal:**
  - Acute glomerulonephritis
  - Renal crises from collagen vascular diseases
  - Severe hypertension following renal transplantation
- Excessive circulating catecholamines:**
  - Pheochromocytoma
  - Tyramine containing foods or drug interactions with MAOIs
  - Sympathomimetic drug use (e.g. cocaine)
  - Rebound HTN after cessation of anti-hypertensive drugs (e.g. clonidine)
- Eclampsia**
- Surgical:**
  - Severe HTN prior to emergent surgery
  - Severe post-op HTN
  - Post-op bleeding from vascular suture lines
- HTN following severe burns**
- Severe epistaxis**

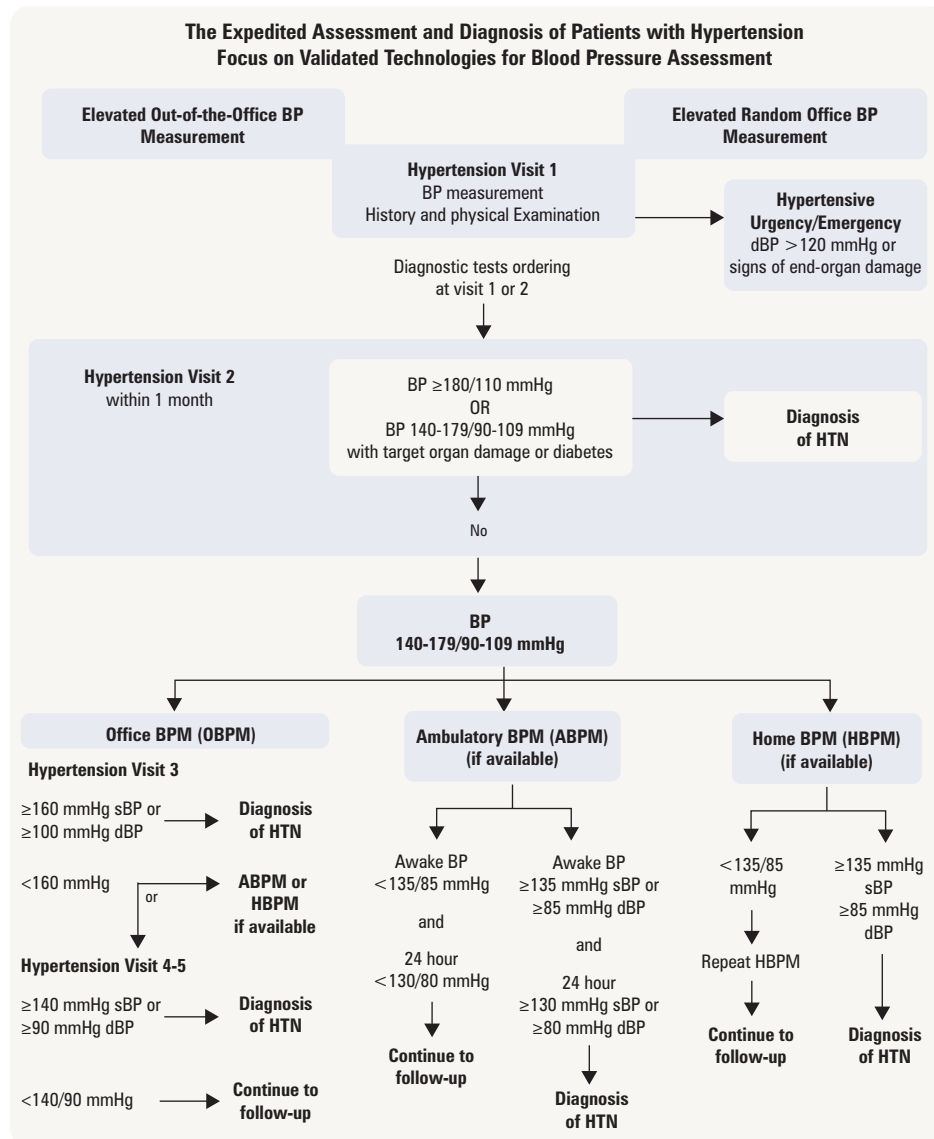


### Causes of Secondary Hypertension

#### ABCDE

Apnea, Aldosteronism  
 Bruits, Bad kidneys  
 Coarctation, Cushing's, Catecholamines,  
 Calcemia  
 Drugs  
 Endocrine disease

## Diagnosis



**Figure 12. Approach to hypertension** Adapted from: CHEP 2013 Guidelines

## Treatment

- target BP is <140/90 mmHg, <130/80 mmHg if DM
- lifestyle modification (in all HTN patients)
  - may be sufficient in patients with stage 1 HTN (140-159/90-99)
  - diet
    - ♦ follow Canada's Guide to Healthy Eating (see *Nutrition*, FM5) and Dietary Approaches to Stop Hypertension (**DASH**) (reduced cholesterol and saturated fats)
    - ♦ limit daily sodium intake to 65-100 mmol (1.5-2.3 g)
    - ♦ potassium/magnesium/calcium supplementations are NOT recommended for HTN
  - moderate intensity dynamic exercise: 30-60 min, 4-7 x/wk; higher intensity exercise is no more effective
  - smoking cessation
  - stress management
  - low-risk alcohol consumption (see *Alcohol*, FM12)
  - achieve and maintain a healthy BMI and waist circumference; BP will decrease by 4.0/2.8 mmHg for each 4.4 kg of weight loss; use multidisciplinary approach to weight loss
  - individualized cognitive behavioural interventions for stress management
- pharmacological
  - indications regardless of age (caution with elderly patients)
    - ♦ dBP ≥90 mmHg with target organ damage or independent cardiovascular risk factors
    - ♦ dBP ≥100 mmHg or sBP ≥160 mmHg without target organ damage or cardiovascular risk factors
    - ♦ sBP ≥140 with target organ damage



### The Effects of Lifestyle Modification on Diet, Weight, Physical Fitness and Blood Pressure Control. 18-month Follow-up Results from the PREMIER Collaborative Research Group

*Ann Intern Med* 2006;144:485-495

**Purpose:** To compare effects of 2 lifestyle modification interventions compared to advice only on hypertension status, blood pressure, and lifestyle changes.

**Study:** Multicentre, randomized trial.

**Patients:** 810 adults with prehypertension or stage 1 hypertension (sBP 120-159, dBP 80-95).

**Interventions:** Multicomponent behavioural intervention using established recommendations ("established") arm, established recommendations plus the Dietary Approaches to Stop Hypertension (DASH) diet ("established + DASH") arm, and advice only arm.

**Main outcomes:** Lifestyle status and blood pressure.

**Results:** At 18 mo, absolute blood pressures were reduced for both intervention arms compared to advice only but differences were non-significant. The odds for HTN at 18 mo were reduced for both treatment arms compared to advice only. Statistically significant weight loss, fat intake and sodium intake were noted for both treatment arms.



### Dieting to Reduce Body Weight for Controlling Hypertension in Adults

*Cochrane DB Syst Rev* 2008;4:CD000484

A systematic review of 18 trials showed that weight-reducing diets in overweight hypertensive persons can affect modest weight loss in the range of 3-9% of body weight and are probably associated with modest blood pressure decreases of roughly 3 mmHg systolic and diastolic. Weight-reducing diets may decrease dosage requirements of persons taking antihypertensive medications.



- first line antihypertensives: thiazide, ACEI, ARB, CCB,  $\beta$ -blocker (if age <60)
- if partial response to standard dose monotherapy, add another first-line drug
- caution with combination of non-DHP CCB and  $\beta$ -blocker
- combination of ACEI and ARB is **not** recommended
- if still not controlled or adverse effects, can add other classes of anti-hypertensives

**Table 30. Pharmacologic Treatment of Hypertension in Patients with Unique Conditions**

Condition or Risk Factor	Recommended Drugs	Alternative Drugs	Not Recommended/Notes
<b>Isolated Diastolic HTN</b>	Thiazide diuretic, $\beta$ -blocker, ACEI, ARB, or long-acting CCB (consider ASA and statin in select patients)	Combinations of first-line drugs	$\beta$ -blocker monotherapy (age >60) or combination of ACEI with an ARB
<b>Isolated Systolic HTN</b>	Thiazide diuretic, ARB or long acting dihydropyridine CCB	Combinations of first-line drugs	Same as above
<b>Coronary Artery Disease</b>	ACEI or ARB; $\beta$ -blocker for patients with stable angina	Long acting CCB, when combination therapy for high risk patients, ACEI/ DHP CCB is preferred	Short-acting CCB (nifedipine) or ACEI + ARB is not recommended
<b>Prior MI</b>	$\beta$ -blocker + ACEI (ARB if can't tolerate ACEI)	Long-acting CCB	ACEI + ARB combination is not recommended
<b>Left Ventricular Hypertrophy</b>	ACEI, ARB, thiazide, or long-acting CCB	Combination of additional agents	Hydralazine and minoxidil can increase LVH, thus not recommended
<b>Cerebrovascular Disease (stroke/TIA)</b>	ACEI + diuretic	Combination of additional agents	ACEI + ARB combination after a stroke is not recommended
<b>Heart Failure</b>	ACEI (ARB if ACEI intolerant) and $\beta$ -blocker Spironolactone in patients with NYHA class II-IV	ARB in addition to ACEI. Hydralazine/isosorbide dinitrate combination if ARB or ACEI not tolerated/contraindicated Thiazide or loop diuretic is recommended as additive therapy	Non-DHP CCB not recommended Carefully monitor for side effects if using ACEI + ARB
<b>Dyslipidemias</b>	Does not affect initial treatment recommendations	Combination of additional agents	
<b>Diabetes Mellitus with Albuminuria (ACR &gt;2.0 mg/mmol in men and &gt;2.8 mg/mmol in women)</b>	ACEI or ARB	Add thiazide diuretic, cardioselective $\beta$ -blocker, long acting CCB	If serum Cr >150 $\mu$ mol/L, a loop diuretic should be considered instead of low-dose thiazide diuretic
<b>Diabetes Mellitus without Albuminuria (criteria listed above)</b>	ACEI, ARB, DHP CCB, or thiazide diuretic	Combination of first-line drugs or, first-line agents not tolerated, cardioselective $\beta$ -blocker or non-DHP CCB	ACEI + ARB combination not recommended
<b>Non-diabetic Chronic Kidney Disease with Proteinuria (urinary protein &gt;500 mg/24 h or ACR &gt;30 mg/mmol)</b>	ACEI (ARB if ACEI intolerant), diuretic as additive therapy	Thiazide for additive antihypertensive therapy, loop diuretic for volume overload	ACEI + ARB combination is not recommended
<b>Renovascular Disease</b>	Same as HTN without other indications		Caution in using ACEI or ARB – monitor for AKI
<b>Asthma</b>	K <sup>+</sup> -sparing + thiazide diuretic for patients on salbutamol		$\beta$ -blocker, unless specific indications like angina or post-MI
<b>Gout</b>			Thiazide, but asymptomatic hyperuricemia is not a contraindication
<b>Smoking</b>	Low dose thiazide ACEI		$\beta$ -blocker
<b>Pregnancy</b>	Methyldopa Hydralazine	Labetolol Nifedipine	ACEI
<b>Elderly (&gt;60)</b>	As for uncomplicated isolated diastolic HTN, except for use of $\beta$ -blocker		$\beta$ -blocker not recommended as first line treatment
<b>Emergency</b>	BP >169/90 = labetalol, nifedipine		
<b>If &gt;3 cardiovascular risk factors or established atherosclerotic disease</b>	Statin, ASA		Caution with use of ASA in patients with uncontrolled BP

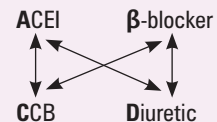
Adapted from: McAlister FA, Zarnke KB, Campbell NRC, et al. The 2001 Canadian recommendations for the management of hypertension: Part two – Therapy. Can J Cardiol 2002;18:625-641 and The 2012 Canadian Hypertension Education Program Recommendations

**Calcium Channel Blockers****Dihydropyridine CCBs**

- amlodipine
- nifedipine
- felodipine

**Non-dihydropyridine CCBs**

- diltiazem
- verapamil

**How to Combine Antihypertensive Medications (in general)****Thiazides as First-Line Antihypertensive Therapy – ALLHAT**

JAMA 2002;288:2981-2997

**Study:** Randomized, double-blind, active-controlled clinical trial with mean follow-up of 4.9 yr.

**Patients:** 33,357 participants (mean age 67y, 53% male, 47% white) with stage 1 or 2 hypertension and at least one other CHD risk factor.

**Intervention:** Participants were randomly assigned to receive chlorthalidone (12.5-25 mg/d), amlodipine (2.5-10mg/d), or lisinopril (10-40 mg/d). Target BP was <140/90 mmHg, achieved by titrating the assigned study drug, and adding open-label agents when necessary.

**Outcomes:** The primary outcome was combined fatal CHD or non-fatal MI. Secondary outcomes were all-cause mortality, stroke, combined CHD, and combined CVD.

**Results:** There were no significant differences in either the primary outcome or all-cause mortality between treatment groups. For amlodipine vs. chlorthalidone, secondary outcomes were similar except for a higher 6-yr rate of heart failure with amlodipine (10.2% vs. 7.7%; p<0.001). For lisinopril vs. chlorthalidone, lisinopril had higher 6-yr rates of combined CVD (33.3% vs. 30.9%; p<0.001), stroke (6.3% vs. 5.6%; p=0.02) and heart failure (8.7% vs. 7.7%; p<0.001).

**Conclusion:** Thiazide-type diuretics are superior to CCB and ACEI for preventing one or more major forms of CVD, with similar risks of death and non-fatal MI.

**ACEI**

Not recommended as monotherapy in people of African descent.

**Follow-Up**

- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification → q3-6mo
- pharmacological
  - q1-2mo until BP under target for 2 consecutive visits
  - more often for symptomatic HTN, severe HTN, antihypertensive drug intolerance, target organ damage
  - q3-6mo once at target BP
- referral is indicated for cases of refractory hypertension, suspected secondary cause or worsening renal failure
- hospitalization is indicated for malignant hypertension

**Low Back Pain**

- see [Orthopedics](#), OR22
- see [www.bigbackpain.com](http://www.bigbackpain.com) for more information

**Definition**

- acute: <6 wk
- subacute: 6-12 wk
- chronic: >12 wk

**Epidemiology**

- 5th most common reason for visiting a physician
- lifetime prevalence: 90%
- peak prevalence: age 45-60
- largest WSIB category
- most common cause of chronic disability for individuals <45 yr old
- 90% resolve in 6 wk, <5% become chronic

**Etiology**

- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes
  - pain is worse with movement, better with rest
  - sprain (ligament), strain (muscle), facet joint degeneration, disc degeneration/herniation, spinal stenosis (e.g. spondylosis), spondylolisthesis, compression fracture, pregnancy
- 2% are non-mechanical causes
  - most concerning when pain is worse at rest and does not change with position
  - surgical emergencies:
    - ♦ cauda equina syndrome (areflexia, lower extremity weakness, decreased anal tone, saddle anesthesia, fecal incontinence, urinary retention), AAA (pulsatile abdominal mass)
  - medical conditions:
    - ♦ neoplastic (primary, metastatic, multiple myeloma)
    - ♦ infectious (osteomyelitis, TB)
    - ♦ metabolic (osteoporosis, osteomalacia, Paget's disease)
    - ♦ rheumatologic (ankylosing spondylitis, polymyalgia rheumatica)
    - ♦ referred pain (perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster)

**Physical Exam**

- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes, sensation)
- posture, gait, ROM and peripheral pulses
- percussion of spine to illicit fracture or infection
- special tests
  - straight leg raise (positive if pain at <70 degrees and aggravated by ankle dorsiflexion), positive test is indicative of sciatica
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy

**Investigations**

- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI

**Red Flags for Back Pain**

Bowel or bladder dysfunction  
Anesthesia (saddle)  
Constitutional symptoms/malignancy  
Chronic disease  
Paresthesias  
Age >50 and mild trauma  
IV drug use/Infection  
Neuromotor deficits

**Yellow Flags for Back Pain**

Psychosocial barriers to recovery that may indicate the risk of long-term disability and work loss

- Belief that pain and activity are harmful
- Negative or low mood, social withdrawal
- Problems with claim and compensation
- History of back pain, time off, and/or other claims
- Poor job satisfaction
- Overprotective family or lack of support
- Persistent pain for 4-6 wk with little to no improvement in symptoms

**Indications for Lumbar Spine X-ray**

- No improvement after 6 wk
- Fever >38°C
- Unexplained weight loss
- Prolonged corticosteroid use
- Significant trauma
- Progressive neurological deficit
- Suspicion of ankylosing spondylitis
- History of cancer (rule out metastases)
- Alcohol/drug abuse (increased risk of osteomyelitis, trauma, fracture)

### Treatment

- reassurance and education if no underlying serious condition
  - 70% improve in 2 wk, 90% in 6 wk
- conservative
  - limited bed rest (>2-4 d bed rest has no proven efficacy and potentially debilitating effects)
  - stay active and continue usual activities, including work, within limits of pain (leads to more rapid recovery and less chronic disability)
  - notes for work or WSIB to endorse “modified, appropriate work” vs. time off
  - heat or cold packs
  - massage may be beneficial, acupuncture may be a helpful adjunct
  - no proven efficacy of spinal traction, spinal manipulation, TENS
- pharmacological
  - preferably taken at intervals
  - acetaminophen (1st line), NSAIDs (2nd line)
  - short-term muscle relaxant use (<7 d) may be helpful (alone or in addition to NSAIDs), but are no better than NSAIDs and may cause drowsiness, dizziness, and dependency
  - do not prescribe opioids
- if no improvement after one month of conservative treatment, consider further investigations
  - imaging and appropriate screening in the presence of any red flags
- surgical evaluation if
  - suspected cauda equina syndrome or AAA
  - worsening neurologic deficit
  - intractable pain not responding to conservative treatment

**Table 31. Approach to Non-traumatic Low Back Pain**

	<b>Back dominant</b> (Pain greatest above gluteal fold)		<b>Leg dominant</b> (Pain greatest below gluteal fold)	
<b>History</b>	<b>Pattern 1</b> Worse with flexion Constant/intermittent	<b>Pattern 2</b> Worse with extension Never worse with flexion Always intermittent	<b>Pattern 3</b> Pain changes with back movement/position Currently/previously constant	<b>Pattern 4</b> Worse with activity Improves with rest and posture change Intermittent/short duration
<b>Physical Exam</b>	Normal neuro exam <u>Fast responder</u> • Improves with extension <u>Slow responder</u> • No change or worsens with extension	Normal neuro exam ± improves with flexion	Leg pain can improve but not disappear Positive straight leg raise ± conduction loss <u>Fast responder</u> • Improves with specific back position <u>Slow responder</u> • Not better with position changes	No irritative findings ± conduction loss
<b>Likely Pathology</b>	Arising from intervertebral discs or adjacent ligaments	Posterior joint complex (associated ligaments and capsular structures)	Sciatica	Neurogenic claudication
<b>Initial Management</b>	Scheduled extension Lumbar roll Night lumbar roll Medication as required	Scheduled flexion Limited extension Night lumbar roll Medication as required	Prone extension Supine “Z” lie Lumbar roll Night lumbar roll Medication as required	Abdominal exercises Night lumbar roll Sustained flexion Medication as required

Adapted from: American Academy of Orthopaedic Surgeons. Acute Care: Nontraumatic Low Back Pain. Orthopaedic Knowledge Update: Spine 2 2001;153-166



#### Massage for Low Back Pain

*Cochrane DB Syst Rev 2008;4:CD001929*

This meta-analysis of 13 randomized trials assessed the use of massage therapy for non-specific low back pain compared to other active or sham treatments.

**Reviewer's Conclusions:** For some patients with subacute or chronic non-specific low back pain, massage may be beneficial, especially with education and exercises. Some evidence suggests that acupuncture massage may be more effective than classic massage but more studies are required to confirm these results.



#### Spinal Manipulative Therapy for Low Back Pain

*Cochrane DB Syst Rev 2004;1:CD000447*

**Methods:** Systematic review of 39 RCTs that compared spinal manipulative therapy with other therapies for low back pain.

**Findings:** For acute and chronic low back pain, spinal manipulative therapy was superior only to sham therapy or therapies judged to be ineffective or even harmful. It had no statistical or clinical advantage over analgesics, physical therapy, exercises, back school, or physician care.

**Conclusions:** For acute and chronic low back pain, there is no evidence that spinal manipulative therapy is superior to other treatments.



#### Non-steroidal Anti-inflammatory Drugs for Low Back Pain

*Cochrane DB Syst Rev 2008;1:CD000396*

This systematic review of 65 randomized and double-blind controlled trials assessed the effects of NSAIDs in treating non-specific low back pain and whether one type of NSAID was more effective.

**Reviewer's Conclusions:** In acute and chronic low back pain without sciatica, NSAIDs are slightly effective for short-term symptomatic relief. There was no difference between NSAIDs and placebo in patients with acute sciatica. No specific type of NSAID appears to be better.



## Menopause/Hormone Replacement Therapy (HRT)

- see [Gynecology](#), GY32

### Epidemiology

- mean age of menopause = 51.4 yr
- a woman will spend over 1/3 of her life in menopause

### Clinical Features

- associated with estrogen deprivation
- urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
- blood vessels and heart: vasomotor instability (e.g. hot flashes), increased risk of heart disease
- bones: bone loss, joint/muscle/back pain, fractures, loss of height
- brain: depression, irritability, mood swings, memory loss

## Management

- encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1200-1500 mg/d) and vitamin D (800-2000 IU/d)
- hormone replacement therapy (HRT)
  - prescribe for moderate to severe symptoms for no longer than 5 yr; routine use is not recommended
  - regimens: cyclic estrogen-progestin, continuous estrogen-progestin, estrogen only (if no uterus), estrogen patch/gel/cream/ring/vaginal tablet
  - decreases risk of osteoporotic fractures, colorectal cancer
  - increases risk of breast cancer, coronary heart disease, stroke, DVT, and PE
  - initiation of HRT requires a thorough discussion of short- and long-term benefits and risks
- consider venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

## Osteoarthritis

- see [Rheumatology](#), RH5



## Epidemiology

- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

## Clinical Features

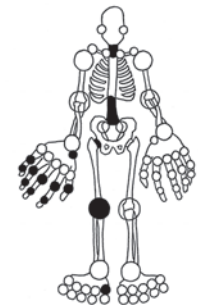
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, peri-articular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

## Investigations

- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

## Management

- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (OT/PT), assistive devices (e.g. canes, orthotics, raised toilet seats)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs in the lowest effective dose for the shortest duration of time, along with gastroprotection; COX-2 selective inhibitors (celecoxib/Celebrex®, Meloxicam/Mobicox®) are recommended if long-term treatment or if high risk for serious GI problems
  - combination analgesics (e.g. acetaminophen and codeine)
  - intra-articular hyaluronic acid injections
  - intra-articular corticosteroid injections (no more than 3-4x/yr) may be helpful in acute flares (benefits last 4-6 wk, can be up to 6 mo)
  - topical NSAID (diclofenac/Pennsaid®)
  - capsaicin cream (Zostrix®)
  - oral glucosamine
- surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)



- Hand (DIP, PIP, 1st CMC)
- Hip
- Knee
- 1st MTP
- L-spine (L4-L5, L5-S1)
- C-spine
- Uncommon: ankle, shoulder, elbow, MCP, rest of wrist

© Linda Colati

**Figure 13. Common sites of involvement in OA**



### Glucosamine Therapy for Treating Osteoarthritis

*Cochrane DB Syst Rev 2005;2:CD002946*

This meta-analysis of 25 single- and double-blinded randomized controlled trials with 4963 patients compared glucosamine treatment, administered by any route, against placebo or another treatment.

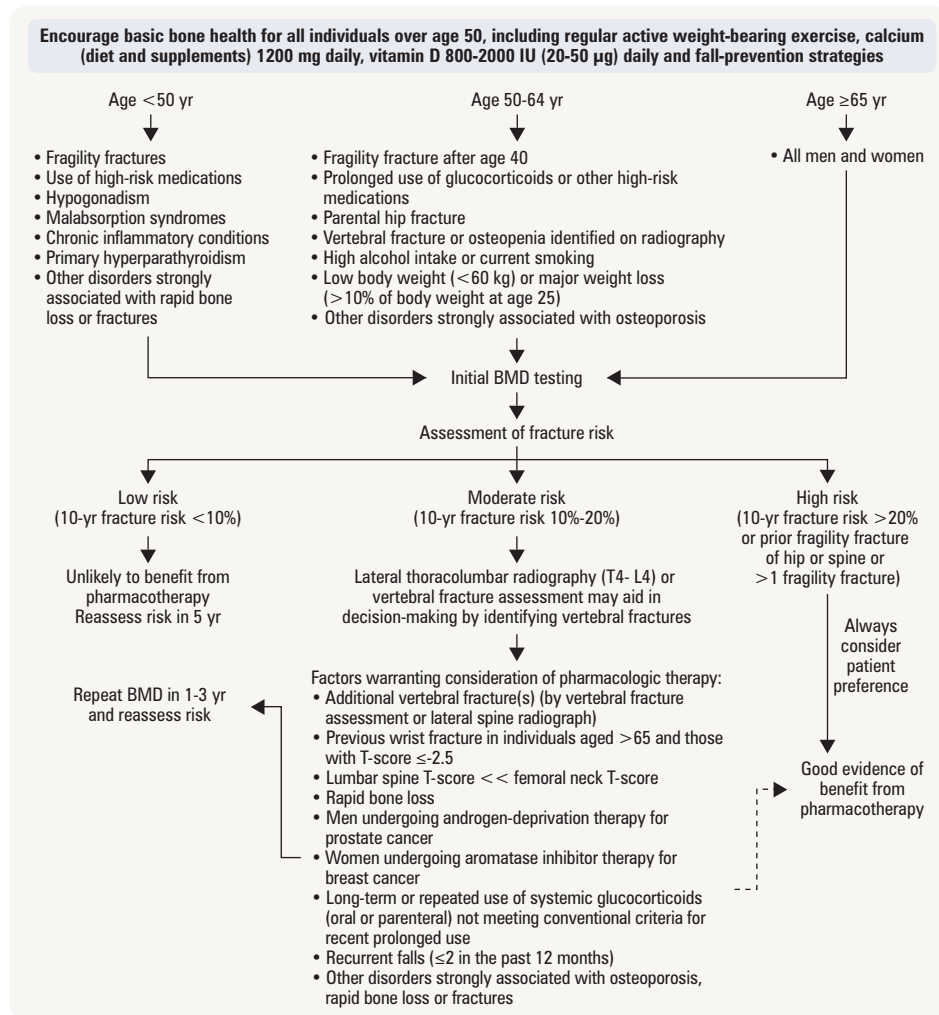
**Reviewer's Conclusions:** Glucosamine can decrease pain and functional impairment resulting from OA and is not associated with any side effects compared to placebo. Differences in the effectiveness of Rotta and non-Rotta preparations highlight variability between glucosamine preparations and patients should be made aware of this.

## Osteoporosis

- see [Endocrinology](#), E42



- for current guidelines see [www.osteoporosis.ca](http://www.osteoporosis.ca)
- age-related disease characterized by decreased bone mass and increased susceptibility to fractures
- affects 1 in 4 Canadian women and 1 in 8 Canadian men



**Figure 14. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (integrated management model).** Adapted from CMAJ 2010;182:1864-1873

### Management

- falls prevention: home safety assessment, optimize vision (e.g. cataract removal), consider hip protectors in older adults living in long-term care facilities
- exercise: weight-bearing, balance, and strengthening exercises as appropriate for the patient's age and functional capacity
- habits: smoking cessation, decrease alcohol intake
- diet: calcium 1200 mg/d through diet and supplements; vitamin D 400-1000 IU/d if healthy and at low risk of deficiency, 800-2000 IU/d if >50 yr and moderate risk of deficiency
- pharmacological
  - vertebral, hip, and non-vertebral fractures: bisphosphonates (alendronate, risedronate, zoledronate), monoclonal Ab (denosumab), estrogen (first line in women with menopausal symptoms)
  - vertebral fractures only: SERM (raloxifene)

**Table 32. First-line Therapies with Evidence for Fracture Prevention in Postmenopausal Women**

Type of Fracture	Antiresorptive Therapy						Bone Formation Therapy
	Bisphosphonates			Denosumab	Raloxifene	Estrogen	
	Alendronate	Risedronate	Zoledronate				Teriparatide
Vertebral	✓	✓	✓	✓	✓	✓	✓
Hip	✓	✓	✓	✓	–	✓	–
Non-vertebral	✓	✓	✓	✓	–	✓	✓

Adapted from CMAJ 2010;182:1864-1873



### Disorders Strongly Associated with Osteoporosis include:

Primary hyperparathyroidism, DM1, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g. IBD)

### 10-yr Fracture Risk Assessment

FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population



### How much Calcium do we Need?

Age	Calcium (mg)
4-8	1000 mg
9-18	1300 mg
19-50	1200 mg
>50	1200 mg
Pregnant and lactating women >18	1000 mg



### Calcium Content of Common Foods

- 1 cup milk = 300 mg
- ¾ cup yogurt = 332 mg
- ½ can salmon with bones = 240 mg
- ½ cup cooked broccoli = 33 mg
- 1 medium orange = 50 mg



### Vitamin D Content in Food

- Milk fortified with vitamin D<sub>3</sub> contains 100 IUs per 250 mL glass.
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish and fish oils (halibut and cod liver oils) all contain small amounts. Supplementation is necessary to obtain adequate levels as dietary intake has minimal impact.
- Most multivitamins provide 400 IUs of vitamin D<sub>3</sub>

- for postmenopausal women, ✓ indicates first-line therapies (grade A)
- for men, alendronate, risedronate, and zoledronate can be used as first-line therapies for prevention of fractures (grade D)
- non-vertebral fractures: hip, femur, pelvis, tibia, humerus, radius, clavicle
- estrogen can be used as first-line therapy in women with menopausal symptoms but the risks may outweigh the benefits (see [Gynecology](#), GY33)
- reflux, esophagitis, and esophageal ulcers are the major side effects of oral bisphosphonates



## Rash

- see [Dermatology](#), D5



### ATOPIC DERMATITIS

- clinical features
  - affects all ages but is more common in children
  - pruritus is the most common symptom; scratching worsens the rash, creating a vicious cycle
- treatment
  - goals: limit itching, repair skin
  - moisturizers, emollients, topical corticosteroids; oral corticosteroids and topical calcineurin inhibitors may be used

### SEBORRHEIC DERMATITIS

- clinical features
  - affects all ages but is most common in infants within the first 3 mo of life (e.g. pityriasis capitis or “cradle cap”) and adults age 30-60 yr
  - affects the scalp, central face, and anterior chest; often presents as scalp scaling (dandruff) in adolescents and adults
  - may cause mild to marked erythema of the nasolabial fold, often with greasy scaling
- treatment
  - topical antifungals, topical low-potency steroids; topical calcineurin inhibitors may be used

### ROSACEA

- clinical features
  - stages: (1) facial flushing, (2) erythema and/or edema and ocular symptoms, (3) papules and pustules, (4) rhinophyma
- treatment
  - topical or oral antibiotics, oral retinoids
  - laser treatment may be an option for progressive telangiectasis or rhinophyma
  - referral may be required to manage rhinophyma, ocular complications, or severe disease

### ACNE VULGARIS

- clinical features
  - types: (I) comedonal, (II) papular, (III) pustular, (IV) nodulocystic
  - predilection for the face, neck, upper chest, and back
- treatment
  - mild acne: topical treatments (antibiotics, benzoyl peroxide, retinoids)
  - moderate acne: after topical treatments have failed, add oral antibiotics and consider hormonal therapy
  - severe acne: consider systemic retinoids

### ONYCHOMYCOSIS (TINEA UNGUIUM)

- definition: fungal infection of the nail bed, matrix, or plate
- clinical features
  - occurs primarily in adults, most commonly after age 60 yr
  - crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris; toenails are affected more often than fingernails
- investigations
  - microscopy of subungual scrapings under KOH preparation, culture
- treatment
  - oral antifungals (terbinafine/Lamisil®, itraconazole/Sporanox®), topical antifungals (ciclopirox/Loprox®)



## Rhinorrhea

- see [Otolaryngology](#), OT22

### Differential Diagnosis

- common cold, sinusitis, influenza, strep pharyngitis, ear infection, vasomotor rhinitis
- allergies, contact with substances, tearing
- foreign body
- opioid withdrawal
- basilar skull fracture

### Investigations

- CBC, throat swab, nasopharyngeal swab, x-ray if injury, allergy testing

### Management

- nasal saline rinse
- consider medications: antihistamines, decongestants, corticosteroid nasal spray



## Sexually Transmitted Infections (STIs)

- see [Gynecology](#), GY26

### Definition

- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

### Epidemiology

- high incidence rates worldwide
- Canadian prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes (increasing incidence of chlamydia and gonorrhea)
  - less common: hepatitis B, HIV and syphilis (both increasing in incidence), trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venereum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

### History

- sexual history
  - age of first intercourse, sexual orientation, sexual activity (oral, anal, and/or vaginal intercourse), sexual activity during travel
  - total number of partners in the past year/month/week and duration of involvement with each
- STI history
  - STI awareness, contraception, previous STIs and testing (including pap tests), partner communication regarding STIs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

### Investigations/Screening

- individuals at increased risk, even those who are asymptomatic, should be screened for chlamydia, gonorrhea, hepatitis B, HIV, and syphilis
- Pap test if none performed in the preceding 12 mo

### Management

- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune, offer Gardasil® to women under age 26
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use condoms or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- an STI patient is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients should abstain from sexual activity until treatment completion and for 1 mo afterwards or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis



#### STI Risk Factors

- Sexually active males and females <25 yr old
- Unprotected sex, sexual contact with a known case of STI, previous STI
- New sexual partner or >2 sexual partners in the past 12 mo
- Street involved, homeless, and/or substance abuse



When an STI is detected in a prepubertal child, evaluation for sexual abuse is mandatory.



#### Prophylactic Vaccination Against Human Papillomavirus Infection and Disease in Women: A Systematic Review of Randomized Controlled Trials

CMAJ 2007;177:469-479

**Purpose:** To evaluate prophylactic HPV vaccination in preventing high- and low-grade cervical lesions, persistent HPV infection, external genital lesions, adverse events, and death using meta-analysis.

**Studies:** 9 reports from 6 different trials with 40,323 patients were included and all studies were of high methodologic quality. Three studies used the quadrivalent vaccine, two used the bivalent, and one used a monovalent. The longest mean duration of follow-up was 48 mo.

**Results:** Prophylactic HPV vaccination decreased the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared to the control group (OR 0.14 (95% CI 0.09-0.21). Vaccinations also prevented persistent HPV infection, low-grade lesions and genital warts and the reported adverse events were mostly minor. Compared to placebo, there was no difference in serious adverse events or death.

**Conclusion:** Prophylactic HPV vaccination is highly efficacious in preventing infection and precancerous cervical disease in women aged 15-25 who have not previously been infected with vaccine-type HPV strains.

Table 33. Diagnosis and Treatment of Common STIs

	Signs and Symptoms	Investigations	Treatment	Complications
<b>Gonococcal Urethritis/Cervicitis</b> ( <i>Neisseria gonorrhoeae</i> )	M: urethral discharge, unexplained pyuria, burning, irritation F: mucopurulent endocervical discharge, vaginal bleeding, dysuria, pelvic pain M and F: often asymptomatic, can involve rectal symptoms in cases of unprotected anal sex	M: urine PCR, urethral swab for gram stain and culture F: urine PCR, endocervical swab for gram stain and culture, vaginal swab for wet mount (to rule out trichomonas) M and F: Urine PCR	Ceftriaxone 250 mg IM single dose F/U in 3-4 wk for test of cure if symptoms persist	M: urethral strictures, epididymitis, infertility F: PID, infertility, ectopic pregnancy, perinatal infection, chronic pelvic pain M and F: Arthritis, increased risk of acquiring and transmitting HIV
<b>Non-Gonococcal Urethritis/Cervicitis</b> (Usually <i>Chlamydia trachomatis</i> **)	~70% asymptomatic If symptoms appear (usually 2-6 wk after infection) then similar to gonococcal symptoms (see above)	Same as above	Azithromycin 1 g PO single dose + gonococcal urethritis/cervicitis Rx* Same F/U as above	Same as above
<b>Human Papilloma Virus</b> (genital warts, cervical dysplasia)	Most are asymptomatic M: cauliflower lesions (condylomata acuminata) on skin/mucosa of penile or anal area F: cauliflower lesions and/or pre-neoplastic/neoplastic lesions on cervix/vagina/vulva	None needed if simple condylomata Potential biopsy of suspicious lesions F: screening for cervical dysplasia through regular Pap smears	For condylomata: cryotherapy, electrocautery, laser excision, topical therapy (patient-applied or office-based) For cervical dysplasia: colposcopy and possible excision, dependent on grade of lesion	M and F: anal cancer MSM and F who have receptive anal sex: rectal cancer F: cervical/vaginal/vulvar cancer
<b>Genital Herpes</b> (HSV-1 and -2)	1° episode: painful vesiculocutaneous genital lesions ± fever, tender lymphadenopathy, protracted course Recurrent episodes: less extensive lesions, shorter course, may have "trigger factors"	Swab of vesicular content for culture, type-specific serologic testing for HSV-1 vs. HSV-2 antibodies and to determine 1° vs. recurrent episode	<u>1° episode:</u> Acyclovir 200 mg PO 5x/d x 5-10 d Famciclovir 250 mg PO tid x 5 d Valacyclovir 1000 mg PO bid x 10 d <u>Recurrent Episode:</u> Acyclovir 200 mg PO 5x/d x 5d or 800 mg PO tid x 2 d Famciclovir 125 mg PO bid x 5 d Valacyclovir 500 mg PO bid x 3 d or 1000 mg PO OD x 3 d	Genital pain, urethritis, cervicitis, aseptic meningitis, increased risk of acquiring and transmitting HIV
<b>Infectious Syphilis</b> ( <i>Treponema pallidum</i> )	1°: chancre (painless sore), regional lymphadenopathy 2°: rash and flu-like symptoms Latent Phase: asymptomatic 3°: neurologic, cardiovascular, and tissue complications	Specimen collection from 1° and 2° lesions, screen high risk individuals with serologic syphilis testing, universal screening of pregnant women	Benzathine penicillin G IM (dose depends on stage) Notify partners (last 3-12 mo) Continuous F/U and testing until patients are seronegative	Chronic neurologic and cardiovascular sequelae, increased risk of acquiring and transmitting HIV

M = Males; F = Females

\*N.B. if urethritis/cervicitis is suspected, always treat for both gonococcal and non-gonococcal types (i.e. ceftriaxone AND azithromycin)

\*\*Most common reportable STI in Canada

## Sinusitis

- see [Otolaryngology](#), OT24

### Etiology

- viral etiology is more common
- viral: rhinovirus, influenza, parainfluenza
- bacterial: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*

### Management of Acute Sinusitis

- may provide symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical or oral decongestants
- do not prescribe antihistamines
- intra-nasal corticosteroids if diagnosed with mild to moderate acute bacterial sinusitis
- antibiotics and intra-nasal corticosteroids if diagnosed with severe acute bacterial sinusitis
- ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, ≥4 episodes/yr, development of complications (e.g. mucocoele, orbital extension, meningitis, intra-cranial abscess, venous sinus thrombosis)



#### Sinusitis Score

- Maxillary toothache (1)
  - History of coloured nasal discharge (1)
  - No improvement with decongestants (1)
  - Abnormal transillumination (1)
  - Purulent secretion on exam (1)
- Other signs: nasal congestion, facial pain/pressure

#### Probability of Sinusitis By Score

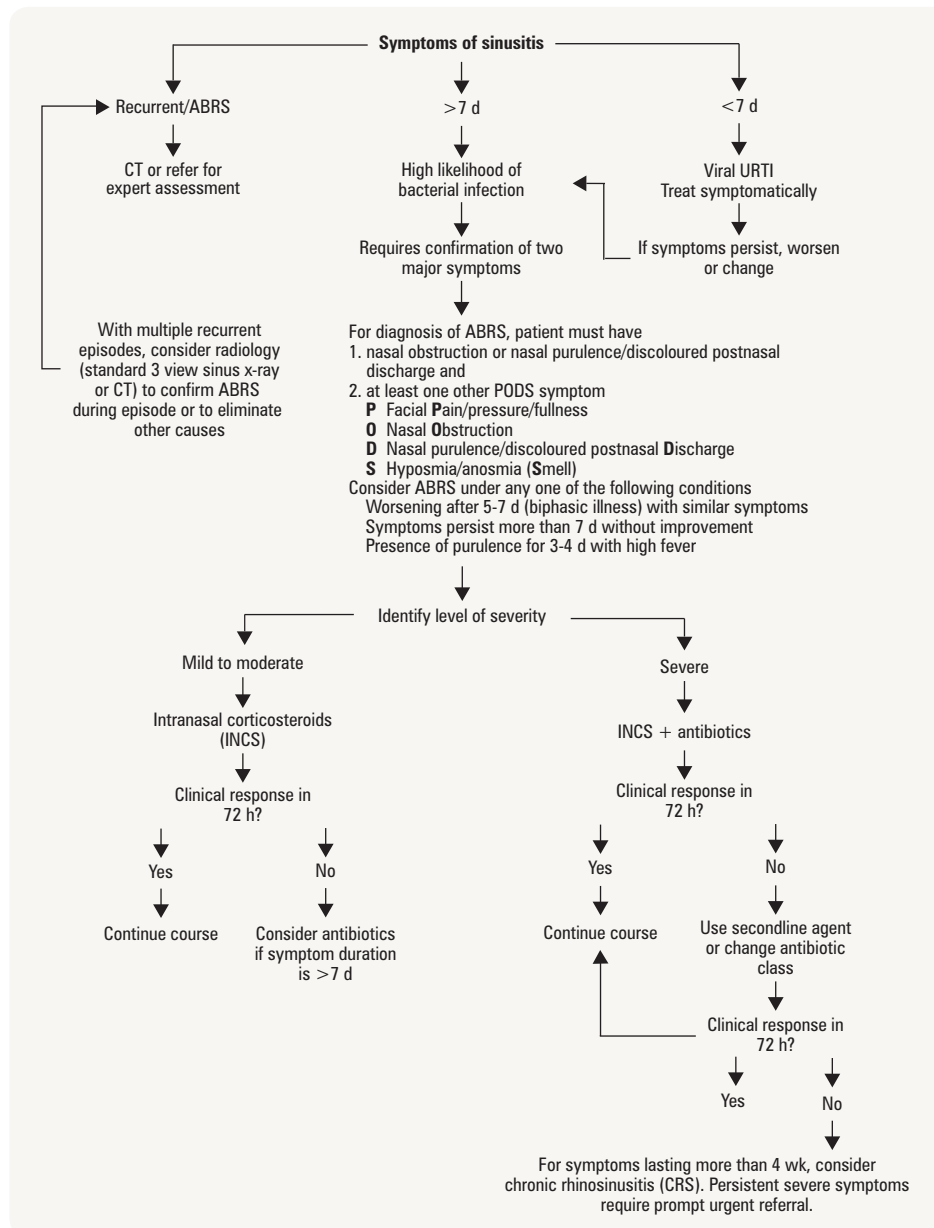
- 0 = 9%
- 1 = 21%
- 2 = 40%
- 3 = 63%
- 4 = 81%
- 5 = 92%

Ebell, MH. *Evidence-based diagnosis: a handbook of clinical prediction rules*. 2001.



#### Red Flags for Urgent Referral

- Altered mental status
- Headache
- Systemic toxicity
- Swelling of the orbit or change in visual acuity or EOM
- Hard neurological findings
- Signs of meningeal irritation
- Suspected intra-cranial complications (meningitis, intra-cranial abscess, cavernous sinus thrombosis)
- Involvement of associated structures (periorbital cellulitis, Pott's puffy tumour)



**Figure 15. Diagnosis and management of sinusitis**

ABRS = acute bacterial rhinosinusitis

Adapted from: Desrosiers M, et al. Allergy Asthma Clin Immunol 2011;7:doi:10.1186/1710-1492-7-2

## Sleep Disorders

- see [Respirology](#), R31 and [Neurology](#), N41

### Definition

- most often characterized by one of three complaints:
  - insomnia
    - ♦ difficulty falling asleep, difficulty maintaining sleep, early-morning wakening, non-refreshing sleep
  - parasomnias
    - ♦ night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
  - excessive daytime sleepiness

### Epidemiology

- 1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems



## Etiology

- primary sleep disorders
  - primary insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, periodic limb movements of sleep
- secondary causes
  - medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD
  - drugs: alcohol, caffeine, nicotine, nicotine replacement therapy,  $\beta$ -agonists, antidepressants, steroids
  - psychiatric: especially mood and anxiety disorders
  - lifestyle factors: shift work

## Investigations

- complete sleep diary every morning for 1-2 wk
  - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (e.g. CBC and differential, TSH)
- refer for sleep study, nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

## Treatment

- treat any suspected medical or psychiatric cause
- psychologic treatment
  - sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
  - exercise regularly, avoid heavy exercise within 3 h of bedtime
  - relaxation therapy: deep breathing, meditation, biofeedback
  - stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
  - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient (improves sleep efficacy)
  - CBT: address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
- pharmacologic treatment
  - short-acting benzodiazepines (e.g. lorazepam, oxazepam, temazepam) at the lowest effective dose should be used <7 consecutive nights to break cycle of chronic insomnia or to manage an exacerbation of previously controlled primary insomnia
  - non-benzodiazepines: zopiclone (Imovane®)
  - F/U every 2-4 wk initially (to reinforce behavioural interventions and renew/consider pharmacotherapy) then every 3 mo; if no progress or limited improvement, consider referral to sleep medicine program

## Specific Problems

- primary insomnia
  - majority of cases
  - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
- snoring
  - results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  - physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)
  - treatment
    - ♦ sleep on side (position therapy), weight loss
    - ♦ nasal dilators (noninvasive external dilator made with elastic adhesive backing applied over nasal bridge), tongue-retaining devices, mandibular advancement devices
  - at risk of developing obstructive sleep apnea
- obstructive sleep apnea (OSA)
  - apnea (no breathing for  $\geq 10$  s) resulting from upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present; leads to a distinctive snoring, choking, awakening type pattern as the body rouses itself to open the airway (resuscitative breath)
  - apneic episodes can last from 20 s to 3 min and occur 100-600 episodes/night
  - diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes per hour of sleep with arousal recorded
  - consequences
    - ♦ daytime somnolence, non-restorative sleep
    - ♦ poor social and work performance



### Risk Factors for Insomnia

- Older age
- Female
- Unemployed or less educated
- Separated or divorced
- Medical comorbidities
- Depression
- Anxiety
- Substance abuse



### Risk Factors for Snoring

- Male
- Obesity
- Alcohol consumption
- Smoking
- Use of tranquilizers or muscle relaxants



### Risk Factors for Obstructive Sleep Apnea

- 2% of women, 4% of men between ages 30-60
- Obesity (due to upper airway narrowing). BMI >28 kg/m<sup>2</sup> present in 60-90% of cases
- Children (commonly due to large tonsils and adenoids)
- Aging (due to decreased muscle tone)
- Persistent URTIs, allergies, nasal tumours, hypothyroidism (due to macroglossia), neuromuscular disease
- Family history

- ♦ mood changes: anxiety, irritability, depression
- ♦ sexual dysfunction: poor libido, impotence
- ♦ morning headache (due to hypercapnia)
- ♦ HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
- ♦ pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
- ♦ memory loss, decreased concentration, confusion
- investigations
  - ♦ evaluate BP, inspect nose and oropharynx (enlarged adenoids or tonsils)
  - ♦ blood gas not helpful, TSH if clinically indicated
  - ♦ nocturnal polysomnography
- treatment
  - ♦ modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
  - ♦ primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
  - ♦ surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy and adenoidectomy (in children)
  - ♦ report patient to Ministry of Transportation if OSA is not controlled by CPAP
- central sleep apnea
  - definition
    - ♦ brain fails to send appropriate signals to the breathing muscles to initiate respirations
    - ♦ defining feature is absent respiratory effort
    - ♦ often secondary to CNS diseases: brainstem infarction, infection, neuromuscular disease
    - ♦ investigations: PFTs, nocturnal polysomnography, MRI
    - ♦ treatment: CPAP or mechanical ventilation (if brainstem origin)
    - ♦ prognosis: poor

## Sore Throat (Pharyngitis)



### Definition

- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

### Etiology

- viral: adenovirus, rhinovirus, influenza virus, RSV, EBV, coxsackie virus, herpes simplex virus, CMV, HIV
- bacterial: group A  $\beta$ -hemolytic *Streptococcus* (GABHS), group C and G  $\beta$ -hemolytic *Streptococcus*, *Neisseria gonorrhoeae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Corynebacterium diphtheriae*

### Epidemiology

- viral
  - most common cause, occurs year round
- bacterial
  - GABHS
    - ♦ most common bacterial cause
    - ♦ occurs most often in winter months
    - ♦ 5-15% of adult cases and up to 50% of all pediatric cases of acute pharyngitis
    - ♦ most prevalent between 5-17 yr old

### Clinical Features

- viral
  - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  - nonspecific flu-like symptoms such as fever, malaise, and myalgia
  - often mimics bacterial infection
  - EBV (infectious mononucleosis)
    - ♦ pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
  - coxsackie virus (hand, foot and mouth disease)
    - ♦ primarily late summer, early fall
    - ♦ sudden onset of fever, pharyngitis, headache, abdominal pain and vomiting
    - ♦ appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
    - ♦ ulcers are pale grey and several mm in diameter, have surrounding erythema, and may appear on hands and feet
  - herpes simplex virus
    - ♦ like coxsackie virus but ulcers are fewer and larger
    - ♦ pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash



### Red Flags in Patients with "Sore Throat"

- Persistence of symptoms longer than 1 wk without improvement
- Respiratory difficulty (particularly stridor, croup, etc.)
- Difficulty in handling secretions (peritonsillar abscess)
- Difficulty in swallowing (Ludwig's angina)
- Severe pain in the absence of erythema (supraglottitis/epiglottitis)
- Palpable mass (neoplasm)
- Blood in the pharynx or ear (trauma)

- bacterial
  - symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
  - signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
  - complications: rheumatic fever, glomerulonephritis, suppurative complications (abscess, sinusitis, otitis media, cervical adenitis, pneumonia), meningitis, impetigo

### Investigations

- suspected GABHS
  - see Table 34 for approach to diagnosis and management of GABHS
  - gold standard for diagnosis is throat culture
  - rapid test for streptococcal antigen: high specificity (95%) but low sensitivity (50-90%)
  - suspected EBV (infectious mononucleosis)
    - ♦ peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or “monospot”)

**Table 34. Modified Centor Score: Approach to Diagnosis and Management of GABHS**

POINTS					
Cough absent?	1				
History of fever >38°C?	1				
Tonsillar exudate?	1				
Swollen, tender anterior nodes?	1				
Age 3-14 yr?	1				
Age 15-44 yr?	0				
Age > 45 yr?	-1				
In communities with moderate levels of strep infection (10-20% of sore throats):					
Score	0	1	2	3	4 or more
Chance patient has strep	1-2.5%	5-10%	11-17%	28-35%	51-53%
Suggested action	NO culture or antibiotic		Culture all, treat with antibiotics only if culture is positive	Culture all, treat with antibiotics on clinical grounds <sup>1</sup> , discontinue antibiotics if culture comes back negative	

<sup>1</sup>Clinical grounds include a high fever or other indicators that the patient is clinically unwell and is presenting early in the course of the illness

Limitations: \*This score is not applicable to patients less than 3 yr of age

\*If an outbreak or epidemic of illness caused by GABHS is occurring in any community, the score is invalid and should not be used

Adapted from: Centor RM et al. Med Decis Making 1981;1:239-46. McIsaac WJ, White D, Tannenbaum D, Low DE. CMAJ 1998;158:75-83

### Management

- viral pharyngitis
  - antibiotics not indicated
  - symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants
- GABHS (see Table 34)
  - antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and suppurative complications
  - incidence of glomerulonephritis is not decreased with antibiotic treatment
  - no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
  - routine F/U and/or post-treatment throat cultures are not required for most patients
  - F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier
- infectious mononucleosis (EBV)
  - self-limiting course; antibiotics are not indicated
  - symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
  - avoid heavy physical activity and contact sports for at least one month or until splenomegaly resolves because of risk of splenic rupture
  - if acute airway obstruction, give corticosteroids and consult ENT



# Complementary and Alternative Medicine (CAM)

## Epidemiology

- 50-75% of Canadians report some use of CAM over their lifetime, and only half will disclose this use to their physician
- use is highest in Western provinces and lowest in Atlantic provinces
- more likely to be used by younger patients and those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy

## Herbal Products

- over 50% of Canadians use natural health products (NHPs)
- most commonly used include echinacea, ginseng, ginkgo, garlic, St. John's Wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  - are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  - are you allergic to any plant products?
  - are you pregnant or breastfeeding?
- information resources: National Center for CAM ([www.nccam.nih.gov](http://www.nccam.nih.gov)), Health Canada website

**Table 35. Common Herbal Products**

Common Name	Reported Uses	Possible Adverse Effects	Possible Drug Interactions
<b>Black cohosh</b>	Menopausal symptoms, PMS, labour induction, arthritis	Hepatitis, liver failure, headaches, GI discomfort, heaviness in legs, weight problems	None reported
<b>Chamomile</b>	Mild sedative, anxiolytic, GI complaints, common cold	Allergic/contact dermatitis, anaphylaxis	Anxiolytics, sedatives
<b>Echinacea</b>	Common cold, flu, wound treatment, urinary tract infections, cancer	Hypersensitivity, hepatotoxicity with prolonged use, avoid use if immunosuppressed	Potentiates warfarin
<b>Evening primrose</b>	Dysmenorrhea, menopausal sx, inflammation, allergies, eczema, arthritis, MS	Headache, restlessness, nausea, diarrhea, may decrease seizure threshold	Anticoagulants, antiplatelets
<b>Feverfew</b>	Migraine prevention, rheumatoid arthritis, anti-inflammatory	Anxiety, upset stomach, skin rash, miscarriage	Anticoagulants, antiplatelets
<b>Flaxseed oil</b>	Laxative, menopausal sx, source of omega-3 fatty acids	Diarrhea	Do not take with other medications as fibre content can bind drugs
<b>Garlic</b>	Elevated lipids, hypertension, hyperglycemia, antimicrobial	GI irritation, contact dermatitis, may increase post-op bleeding	Anticoagulants, potentiates antihypertensives
<b>Ginger</b>	Nausea, motion sickness, dyspepsia, anti-inflammatory	Heartburn, not to be used for morning sickness	None known
<b>Ginkgo biloba</b>	Increases peripheral circulation (AD, dementia, intermittent claudication), premenstrual syndrome, vertigo	Headache, cramping, bleeding, mild digestive problems; reports of intracranial hemorrhage	Anticoagulants, thiazide diuretics, MAO inhibitors
<b>Ginseng</b>	Energy enhancer, decreases stress, adjunct support for chemotherapy/radiation	Hypertension, nervousness, insomnia, breakthrough bleeding, palpitations	Stimulant medications, antihypertensives, hormonal therapies
<b>Glucosamine (Chondroitin)</b>	Osteoarthritis	GI distress, headache, drowsiness, palpitations	Caution if shellfish allergy
<b>Saw palmetto</b>	BPH, adjunct to finasteride	Mild GI distress	$\alpha$ -adrenergics, finasteride
<b>St. John's Wort</b>	Mild to moderate depression	Photosensitivity, increased liver enzymes, drowsiness, dizziness, nausea, headaches	CNS depressants, C/I with indinavir
<b>Valerian root</b>	Sedative, anxiolytic, muscle relaxant, PMS	Drowsiness, headache, digestive problems, paradoxical insomnia	CNS depressants, antihistamines

References: Zink T, Chaffin J. Herbal "health" products: What family physicians need to know, *American Family Physician* 1998;58:1133-1140; NIH National Center for Complementary and Alternative Medicine website (<http://nccam.nih.gov>)



### Most Common Uses of CAM:

- Back/neck problems
- Gynecological problems
- Anxiety
- Headaches
- Digestive problems
- Chronic fatigue syndromes



### St. John's Wort for Depression

*Cochrane DB Syst Rev* 2005;2:CD000448

A meta-analysis of 37 trials, including 26 which compared St. John's Wort with placebo and 14 which compared St. John's Wort with standard antidepressants. The main outcome measure was the ratio of responders to non-responders, and the main outcome measure for adverse effects was the number of patients dropping out due to adverse experiences. Significant heterogeneity was noted among placebo-controlled trials, but trials were statistically homogeneous for trials comparing St. John's Wort with antidepressants. For major depression, compared with placebo, the OR for 6 larger trials was 1.15 (95% CI 1.02-1.29) and 5 smaller trials, 2.06 (95% CI 1.65-2.59). Compared with SSRIs and tricyclics, the response rates were 0.98 (95% CI 0.85-1.12) and 1.03 (95% CI 0.93-1.14), respectively. Fewer patients on St. John's Wort dropped out due to adverse effects compared to those taking tricyclics (OR 0.25; 95% CI 0.14-0.45), and a similar but non-significant trend was seen when compared with SSRIs (OR 0.60; 95% CI 0.31-1.15). Drawing solid conclusions is difficult given the degree of study heterogeneity and number of conflicting studies.

## Primary Care Models

Table 36. Primary Care Models

	Characteristics
<b>Comprehensive Care Model</b>	<ul style="list-style-type: none"> <li>FPs/GPs in solo practice with limited after-hours availability</li> <li>Payment model: fee-for-service</li> </ul>
<b>Family Health Team</b>	<ul style="list-style-type: none"> <li>Groups of health care professionals (e.g. FPs, GPs, RNs, NPs, dieticians, social workers)</li> <li>Wider range of services (e.g. rehabilitation, palliative care), with increased after-hours availability</li> <li>Receives provincial funding for allied health</li> <li>Payment model: paid annually per patient rostered depending on demographic category</li> </ul>
<b>Family Health Group</b>	<ul style="list-style-type: none"> <li>Group of <math>\geq 3</math> FPs, with some after-hours availability as well as on-call to telephone health advisory services</li> <li>Payment model: fee-for-service plus premiums</li> </ul>
<b>Family Health Network</b>	<ul style="list-style-type: none"> <li>Group of <math>\geq 3</math> FPs, can utilize nurse practitioners, with telephone health advisory services to provide around the clock primary care coverage</li> <li>Payment model: salary-based</li> </ul>
<b>Family Health Organization</b>	<ul style="list-style-type: none"> <li>Same as FHT but usually larger in scale in terms of personnel</li> </ul>

## Antimicrobial Quick Reference

Condition	Microorganisms	Antimicrobial
<b>RESPIRATORY/ENT</b>		
<b>Acute Rhinitis</b> (common cold)	Rhinovirus, Coronavirus, Influenza, RSV, Parainfluenza, Adenovirus	None
<b>Pharyngitis</b> (sore throat)	Rhinovirus, Adenovirus, Influenza, Parainfluenza, Coxsackievirus, Coronavirus	None
<b>Strep Pharyngitis</b>	Group A $\beta$ -Hemolytic <i>Strep</i>	<p><b>Children:</b>  <b>1st line:</b> penicillin V 40 mg/kg/d PO div bid-tid (max 750 mg/d) x 10 d (use adult dose if <math>&gt;27</math> kg)            amoxicillin 40 mg/kg/d PO div bid-tid x 10 d  <b>2nd line:</b> erythromycin estolate 40 mg/kg/d PO div bid-tid x 10 d  <b>3rd line:</b> cephalexin 25-50 mg/kg/d PO div qid x 10 d            cefprozil 15 mg/kg/d PO div bid x 10 d</p> <p><b>Adults:</b>  <b>1st line:</b> penicillin V 300 mg PO tid or 600 mg bid x 10 d  <b>2nd line:</b> erythromycin 250 mg PO qid x 10 d  <b>3rd line:</b> cephalexin 250 mg PO qid x 10 d            cefadroxil 500 mg PO bid x 10 d</p>
<b>Sinusitis</b>	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i> <i>S. aureus</i>	<p><b>Children:</b>  <b>1st line:</b> amoxicillin 80 mg/kg/d PO div bid-tid x 5-10 d (max 3 g/d) x 10-14 d  <b>2nd line:</b> amoxicillin/clavulanate 40-80 mg/kg/d div bid (max 3 g/d) x 10-14 d            cefprozil 30 mg/kg/d PO div bid x 10-14 d  <b>3rd line:</b> cefuroxime-AX 30-40 mg/kg/d PO div bid x 10-14 d            clarithromycin 15 mg/kg/d PO div bid x 10-14 d</p> <p><b>Adults:</b>  <b>1st line:</b> amoxicillin 500 mg PO tid x 5-10 d  <b>2nd line:</b> amoxicillin/clavulanate 500 or 875 mg PO bid x 5-10 d            cefuroxime-AX 250-500 mg PO bid x 5-10 d  <b>3rd line:</b> levofloxacin 500 mg PO OD x 5-10 d            moxifloxacin 400 mg PO OD x 5-10 d</p>
<b>Acute Otitis Media</b>	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i> Group A <i>Strep</i> <i>S. aureus</i>	<p><b>Children:</b>            Treat if under age 6 mo            If age 6-24 mo, watchful waiting appropriate if parents can observe child for 48-72 h with appropriate medical follow-up            If age <math>&gt;24</math> mo, treat if worsens after 48-72 h            10 d course if age <math>&lt;24</math> mo, 5 d course if age <math>&gt;24</math> mo  <b>1st line:</b> amoxicillin 80 mg/kg/d PO div bid-tid (max 3 g/d)  <b>2nd line:</b> amoxicillin/clavulanate 40-80 mg/kg/d PO div bid (max 3 g/d)            cefprozil 30 mg/kg/d PO div bid  <b>3rd line:</b> cefuroxime-AX 30-40 mg/kg/d PO div bid            clarithromycin 15 mg/kg/d PO div bid            Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</p> <p><b>Adults:</b>  <b>1st line:</b> amoxicillin 500 mg PO tid x 7-10 d  <b>2nd line:</b> amoxicillin/clavulanate 500 mg PO tid or 875 mg PO bid x 7-10 d            cefprozil 250-500 mg PO bid x 7-10 d            Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid</p>

Condition	Microorganisms	Antimicrobial
<b>RESPIRATORY/ENT</b>		
<b>Otitis Externa</b>	<i>P. aeruginosa</i> Coliforms <i>S. aureus</i>	<u>1st line:</u> Buro-sol <sup>®</sup> otic solution 2-3 drops tid or qid <u>2nd line:</u> Cortisporin <sup>®</sup> otic solution 4 drops tid or qid (3 drops tid or qid for children) TM defect: Ciprodex <sup>®</sup> otic suspension 4 drops bid Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO bid x 4-8 wk
<b>Bronchitis</b>	Influenza, parainfluenza, coronavirus, rhinovirus, RSV	None
<b>Community Acquired Pneumonia: Outpatient without Comorbidity</b>	<i>S. pneumoniae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i>	<u>1st line:</u> amoxicillin 1 g PO tid x 7-14 d (for patients over age 50 yr where mycoplasma infection is less likely) erythromycin 500 mg PO qid x 7-14 d clarithromycin 500 mg PO bid or 1000 mg (ER) PO OD x 7-14 d azithromycin 500 mg PO on 1st d then 250 mg PO OD x 4 d or 500 mg PO OD x 3 d <u>2nd line:</u> doxycycline 100 mg PO on 1st d then 100 mg PO OD x 7-14 d
<b>Community Acquired Pneumonia: Outpatient with Comorbidity</b>	<i>S. pneumoniae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i> <i>H. influenza</i>	<b>ANY ONE of the <math>\beta</math>-lactam agents below:</b> amoxicillin 1000 mg PO tid x 7-14 d amoxicillin/clavulanate 500 mg PO tid or 875 mg PO bid x 7-14 d cefuroxime-AX 500 mg PO bid x 7-14 d cefprozil 500 mg PO bid x 7-14 d <b>PLUS ONE of the following:</b> clarithromycin 500 mg PO bid or 1000 mg (ER) PO OD x 7-14 d azithromycin 500 mg PO OD on 1st d then 250 mg PO OD x 4d doxycycline 100 mg PO bid on 1st d then 100 mg PO OD x 7-14 d <b>OR ANY ONE of the following:</b> levofloxacin 750 mg PO OD x 7-14 d moxifloxacin 400 mg PO OD x 7-14 d
<b>Dental Infections/ Periapical and Periodontal Abscesses</b>	Oral Flora	penicillin V potassium 500 mg PO qid x 7-10 d clindamycin 300 mg PO qid or 600 mg bid x 7-10 d
<b>GASTROENTEROLOGY</b>		
<b>Diarrhea – Enteritis</b>	Enterotoxigenic <i>E. coli</i> (ETEC) <i>Campylobacter</i> <i>Salmonella</i> <i>Shigella</i> Viruses Protozoa	<u>Mild to moderate</u> (i.e. <3 BM/d, no blood, no fever): OTC loperamide 4 mg PO STAT then 2 mg PO after each loose stool (max 8 doses/d) OTC bismuth subsalicylate (Pepto Bismol <sup>®</sup> ) 2 tabs or 30 mL repeat q30min prn (max 8 doses/d) (prevention: 2 tabs or 30 mL qid with meals and in the evening)  <u>Moderate to severe</u> (i.e. >3 BM/d, blood, fever): ofloxacin 400 mg PO single dose or 300 mg PO bid x 3 d (prevention: 300 mg PO OD) norfloxacin 800 mg PO single dose or 400 mg PO bid x 1-3 d (prevention: 400 mg PO OD) ciprofloxacin 750 mg PO single dose or 500 mg PO bid x 1-3 d (prevention: 500 mg PO OD) levofloxacin 500 mg PO OD x 1-3 d (prevention: 500 mg PO OD) azithromycin 1000 mg PO single dose or 500 mg PO OD x 1-3 d (children: 10 mg/kg/d x 3 d)  <i>Azithromycin:</i> Recommended primarily for Thailand, India, Nepal, and Indonesia where <i>Campylobacter</i> resistance to quinolones is high Considered drug of choice for children because of safety, tolerability, and ease of administration
<b>Diarrhea – post abx</b> (common with clindamycin)	<i>C. difficile</i>	<u>Mild to moderate</u> (WBC <5 x 10 <sup>9</sup> /L and Cr <1.5 x baseline): metronidazole 500 mg PO tid or 250 mg PO qid x 10 d (children: 15-30 mg/kg/d PO div tid-qid max 4 g/d)  <u>Severe</u> (WBC $\geq$ 15 x 10 <sup>9</sup> /L and Cr $\geq$ 1.5 x baseline): vancomycin 125 mg PO qid x 10-14 d (children: 40 mg/kg/d PO div tid-qid x 10-14d max 2 g/d)
<b>Peptic Ulcer Disease</b> (non-NSAID related)	<i>H. pylori</i>	<u>PPI:</u> lansoprazole 30 mg or omeprazole 20 mg or pantoprazole 40 mg or rabeprazole 20 mg  <u>1st line:</u> [PPI PO bid + amoxicillin 1000 mg PO bid + clarithromycin 500 mg PO bid x 7 d (e.g. HP-PAC: lansoprazole 30 mg PO bid + amoxicillin 1000 mg PO bid + clarithromycin 500 mg PO bid x 7 d)] [PPI PO bid + metronidazole 500 mg PO bid + clarithromycin 500 mg or 250 mg PO bid x 7 d] <u>2nd line:</u> [PPI PO bid + metronidazole 500 mg PO bid + amoxicillin 1000 mg PO bid x 7 d] [PPI PO bid + bismuth subsalicylate 2 tabs or 30 mL qid + metronidazole 250 mg PO qid + tetracycline 500 mg PO qid x 7-14 d]

Condition	Microorganisms	Antimicrobial
<b>GENITOURINARY</b>		
<b>UTI/Cystitis</b>	<i>Klebsiella</i> <i>E. coli</i> <i>Enterobacter</i> <i>Enterococci</i> <i>Proteus</i> <i>S. saprophyticus</i>	<p><u>1st line:</u> TMP/SMX 2 tabs bid or 1 DS tab bid x 3 d trimethoprim 100 mg PO bid or 200 mg PO OD x 3 d nitrofurantoin 50-100 mg PO qid or Macrobid® 100 mg bid x 5 d</p> <p><u>2nd line:</u> amoxicillin 500 mg PO tid x 7 d norfloxacin 400 mg PO bid x 3 d ciprofloxacin 250 mg PO bid or 500 mg (ER) OD x 3 d</p> <p>NB: high rate of amoxicillin resistance in community <i>E. coli</i>, use only after lab susceptibility obtained</p> <p><u>3rd line:</u> cephalexin 250-500 mg PO qid x 7 d levofloxacin 250 mg PO OD x 3 d</p> <p><u>Pregnancy:</u> cephalexin 250-500 mg PO qid x 7 d nitrofurantoin 50-100 mg PO bid x 5 d amoxicillin 500 mg PO tid x 7 d NB: nitrofurantoin is contraindicated in pregnancy after 36 wk</p>
<b>Head and Pubic Lice (crabs)</b>	<i>Pediculus humanus capitis</i> <i>Phthirus pubis</i>	permethrin cream 1%: apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk
<b>Vulvovaginal Candidiasis</b>	<i>Candida</i>	Treat only if patient is symptomatic fluconazole 150 mg PO single dose miconazole 2% cream (Monistat 7®): one applicator (5 g) intravaginally qhs x 7 d
<b>Bacterial Vaginosis</b>	Overgrowth of: <i>G. vaginalis</i> <i>M. hominis</i> Anaerobes	If patient is asymptomatic, treatment is unnecessary unless high-risk pregnancy, prior IUD insertion, gynecologic surgery, induced abortion, or upper tract instrumentation. <u>1st line:</u> metronidazole 500 mg PO bid x 7 d metronidazole 0.75% gel: one applicator (5 g) intravaginally qhs x 5 d clindamycin 2% cream: one applicator (5 g) intravaginally qhs x 7 d <u>2nd line:</u> metronidazole 2 g PO single dose clindamycin 300 mg PO bid x 7 d
<b>Herpes</b>	Herpes simplex virus	<p><u>1° episode:</u> acyclovir 400 mg PO tid x 5-7 d famciclovir 250 mg PO tid x 5-7 d valacyclovir 500-1000 mg PO bid x 5-7 d</p> <p><u>Recurrent Episode:</u> acyclovir 400 mg PO tid x 5d or 800 mg PO bid x 5 d or 800 mg PO tid x 2 d famciclovir 125 mg PO bid x 5 d valacyclovir 500 mg PO bid x 3 d or 1000 mg PO OD x 3 d</p> <p><u>Pregnancy:</u> 1° episode: acyclovir 200 mg PO 5x/d x 5-10 d Prior infection within previous yr: acyclovir 200 mg PO qid at 36 wk valacyclovir 500 mg PO bid at 36 wk</p>
<b>Gonorrhea/Chlamydia</b>	<i>N. gonorrhoeae</i> <i>C. trachomatis</i>	ceftriaxone 250 mg IM x 1 dose + azithromycin 1 g PO single dose or doxycycline 100 mg PO bid x 7 d
<b>DERMATOLOGIC</b>		
<b>Mastitis</b>	<i>S. aureus</i> <i>S. pyogenes</i>	cloxacillin 500 mg PO qid x 7d cephalexin 500 mg PO qid x 7d
<b>Tinea Cruris/Pedis</b> (jock itch/athlete's foot)	Trichophyton	clotrimazole 1% cream bid ketoconazole 2% cream bid
<b>Uncomplicated Cellulitis</b>	<i>S. aureus</i> Group A <i>Strep</i>	<p><u>Children:</u> <u>1st line:</u> cephalexin 50-100 mg/kg/d div qid x 10-14 d <u>2nd line:</u> cloxacillin 50 mg/kg/d div qid x 10-14 d clindamycin 25 mg/kg/d x 10-14 d</p> <p><u>Adults:</u> <u>1st line:</u> cephalexin 500 mg PO qid x 10-14d <u>2nd line:</u> cloxacillin 500 mg PO qid x 10-14 d clindamycin 300 mg PO x 10-14 d</p>

Condition	Microorganisms	Antimicrobial
<b>OPHTHALMOLOGY</b>		
<b>Viral Conjunctivitis</b>	Adenovirus Coxsackievirus ECHO virus	None NB: very contagious
<b>Bacterial Conjunctivitis</b>	<i>S. aureus</i> <i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i>	Duration is 5-7 d unless otherwise specified All doses should be administered while awake  OTC for adults and children age > 1 yr: gramicidin-polymixin drops (Polysporin® or Optimyxin®): 1 drop q3-4h bacitracin-polymixin ointment (Polysporin® or Optimyxin®): 1/2 inch qid  Prescription for adults and children age > 1 yr: erythromycin 0.5% ointment: 1/2-1 inch qid fucidin 1% drops (children age > 2 yr): 1 drop bid sulfacetamide sodium 10% drops: 1-2 drops q2-3h then taper to bid  Fluoroquinolones preferred for more serious cases, especially suspected <i>Pseudomonas</i> (e.g. contact lens wearers), corneal involvement, or treatment failure: besifloxacin 0.6% drops: 1 drop tid x 7 d ciprofloxacin 0.3% drops: 1-2 drops q2h x 2 d then q4h x 5 d ciprofloxacin 0.3% ointment: 1/2 inch bid-tid gatifloxacin 0.3% drops: 1-2 drops q2h x 2 d then qid x 5 d
<b>Blepharitis</b>	<i>S. aureus</i> <i>S. epidermidis</i> <i>P. acnes</i> <i>Corynebacteria</i>	<u>Lid hygiene</u> : Mainstay of treatment and works best OD or bid <u>Abx ointment</u> : Helpful in short-term of acute phase but resistance rapidly ensues if treatment is prolonged <u>1st line</u> : bacitracin-polymixin ointment (Polysporin® or Optimyxin®): 1/2 inch qhs erythromycin 0.5% ointment: 1/2 inch qhs <u>2nd line</u> : gentamicin 0.3% ointment: 1/2 inch qhs tobramycin 0.3% ointment: 1/2 inch qhs

\*All doses are adult doses unless otherwise specified

\*This chart is not all-encompassing and is non-inclusive of special exceptions (i.e. pregnancy, poor renal clearance, etc.)

\*Comorbidities includes COPD (received steroids within the last 3 mo), liver or renal disease, CHF, diabetes, malignancy, alcoholism, asplenia, immunosuppressing conditions, malnutrition, hospitalization in past 3 mo or nursing home

## References

### Abuse

Fogarty CT, Burge S, McCord E. Communicating with patients about intimate partner violence: screening and interviewing approaches. *Fam Med* 2002;34:369-375.

National Center on Elder Abuse at the American Public Human Services Association. National elder abuse incidence study (internet). Available from: [http://www.aqa.gov/eldfam/Elder\\_Rights/Elder\\_Abuse/AbuseReport\\_Full.pdf](http://www.aqa.gov/eldfam/Elder_Rights/Elder_Abuse/AbuseReport_Full.pdf)  
Wathen CN, MacMillan HL. Interventions for violence against women. *JAMA* 2003;289:589-599.

### Diabetes

Canadian Diabetes Association. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008;32(suppl 1):S56.

Nield L, et al. Dietary advice for treatment of type 2 diabetes mellitus in adults. *Cochrane DB Syst Rev* 2007;Issue 3.

Norris SL, et al. Long-term non-pharmacological weight loss interventions for adults with pre-diabetes. *Cochrane DB Syst Rev* 2005;Issue 2.

Saenz A, et al. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane DB Syst Rev* 2005;Issue 3.

### Diet and Obesity

Calle E, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of US adults. *NEJM* 1999;341:1097-1105.

Canada's Food Guide to Healthy Eating. Health Canada. Last updated 2007.

Lau D, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. *CMAJ* 2007;176:S1-13.

National Institute of Health, National Heart Lung and Blood Institute, Obesity Education Initiative. Classification of overweight and obesity by BMI, waist circumference, and associated disease risks (internet). Available from: [http://www.nhlbi.nih.gov/health/public/heart/obesity/lose\\_wt/bmi\\_dis.htm](http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm).

Dansinger ML, et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction. *JAMA* 2005;293:43-53.

Health Canada. Canada's food guide to healthy eating (internet). Last updated 2005-06-07. Available from: [http://www.hc-sc.gc.ca/n-an/food-guide-aliment/fg-rainbow-arc\\_en\\_cie\\_ga\\_e.html](http://www.hc-sc.gc.ca/n-an/food-guide-aliment/fg-rainbow-arc_en_cie_ga_e.html).

Health Canada. Canada's physical activity guide to healthy active living. Available from: <http://www.hc-sc.gc.ca/hppb/paguide/main.html>.

Krauss RM, et al. AHA dietary guidelines: a statement for healthcare professionals from the nutrition committee of the American Heart Association. (revised 2000). *Stroke* 2000;31:2751-2766.

Lichtenstein AH, et al. Diet and lifestyle recommendations: a scientific statement from the American Heart Association Nutrition committee. (revised 2006). *Circulation* 2006;114:82-96.

### Dyslipidemia, Hypertension and Heart Disease

Canadian Hypertension Education Program. 2009 Canadian hypertension education program recommendations: an annual update. *Can Fam Phys* 2009;55:697-700.

Canadian Hypertension Education Program. 2010 Canadian hypertension education program recommendations for the management of hypertension. *Can J Cardiol* 2010;26:241-258.

Elmer PJ, et al. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. *Ann Intern Med* 2006;144:485-495.

Graham DJ, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004;292:2585-2590.

J Genest, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. *Can J Cardiol* 2009;25:567-579.

Manson JE et al. Estrogen plus progestin and the risk of coronary heart disease. *NEJM* 2003;349:523-34.

McPherson R et al. Canadian Cardiovascular Society position statement – Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol* 2006;22:913-27.

Ontario Drug Therapy Guidelines for Stable Ischemic Heart Disease in Primary Care. Ontario Program for Optimal Therapeutics. Toronto: Queen's Printer of Ontario, 2000:10.

Onusko E. Diagnosing secondary hypertension. *Am Fam Physician* 2003;67:67-74.

Lichtenstein AH, et al. Diet and lifestyle recommendations revision 2006: A scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82-96.

Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: Summary of the 2003 update. *CMAJ*. 2003;169:921-4.

### Smoking

Cahill K, et al. Nicotine receptor partial agonists for smoking cessation. *Cochrane DB Syst Rev* 2008;Issue 3.

Health Canada. Canadian tobacco use monitoring survey (CTUMS): annual results 2008. Available from: [http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc\\_2008-eng.php](http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/ctums-esutc_2008-eng.php)

Hughes JR, et al. Antidepressants for smoking cessation. *Cochrane DB Syst Rev* 2007;Issue 1.

Ontario Medical Association. OMA position paper: rethinking stop-smoking medications. (cited January 2008). Available from: <https://www.oma.org/Resources/Documents/e2008RethinkingStop-Smoking/Medications.pdf>.

Shroeder SA. What to do with a patient who smoked. *JAMA* 2005;294:482-487.

Stead LF, et al. Nicotine replacement therapy for smoking cessation. *Cochrane DB Syst Rev* 2008;Issue 1.  
Stead LF, et al. Physician advice for smoking cessation. *Cochrane DB Syst Rev* 2008;Issue 2.

#### Other

Assendelft WJJ, et al. Spinal manipulative therapy for low-back pain. *Cochrane DB Syst Rev* 2004;Issue 1.  
Bagai A, et al. Does this patient have hearing impairment? *JAMA* 2006;295:416-428.  
Beck E, Sieber WJ, Trejo R. Management of cluster headaches. *Am Fam Phys* 2005;71:17724.  
Bent S, et al. Does this woman have an acute uncomplicated urinary tract infection? *JAMA* 2002;287:2701-2710.  
Bric V, Ebberdt C, Kaczorowski J. Development of a tool to identify poverty in a family practice setting: a pilot study. *Int J Family Med* 2011;2011:812182.  
British Columbia Medical Association and British Columbia Ministry of Health Services. Osteoarthritis in peripheral joints: diagnosis and treatment. Guidelines & Protocol, Advisory Committee, 2008.  
Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167:S1-34.  
Burge SK, Schneider FD. Alcohol-related problems: recognition and intervention. *Am Fam Phys* 1999;59:361-370.  
Canadian Task Force on Preventive Health Care. The canadian guide to clinical preventive health care. Ottawa: Minister of Supply and Services Canada. Available from: <http://www.ctfphc.org>.  
Canadian Task Force on Preventive Health Care. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. *CMAJ* 2011;183:1991-2001.  
Centor RM, et al. The diagnosis of strep throat in adults in the emergency room. *Med Decis Making* 1981;1:239-246.  
Cheung AM, et al. Prevention of osteoporosis and osteoporotic fractures in post-menopausal women: recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ* 2004;170:1665-1667.  
Comuz J, Guessous I, Farrat B. Fatigue: a practical approach to diagnosis in primary care. *CMAJ* 2006;174:765-767.  
David AK, et al. Family medicine: principles and practice, 6th ed. New York: Springer-Verlag, 2003.  
Derby CA, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? *Urology* 2000;56:302-306.  
Desrosiers M, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *Allergy, Asthma & Clin Immunol* 2011;7:doi:10.1186/1710-1492-7-2.  
Domino FJ, et al. The 5-minute clinical consult, 18th ed. Lippincott Williams & Wilkins, 2009.  
Ebell MH. Evidence-based diagnosis: a handbook of clinical prediction rules. Springer, 2001.  
Ebell MH. Treating adult women with suspected UTI. *Am Fam Phys* 2006;73:293-296.  
Edmonds M, et al. Exercise therapy for chronic fatigue syndrome. *Cochrane DB Syst Rev* 2004;Issue 3.  
Evans M (editor). Mosby's family practice sourcebook: an evidence based approach to care, 4th ed. Elsevier Canada, 2006: 343-345.  
Evans M, Bradwejn J, Dunn L. Guidelines for the treatment of anxiety disorders in primary care. Toronto: Queen's Printer of Ontario, 2002.  
Fauci AS, et al. Harrison's Principles of Internal Medicine, 17th ed. McGraw-Hill Professional, 2008.  
Furlan AD, et al. Acupuncture and dry-needling for low back pain. *Cochrane DB Syst Rev* 2005;Issue 1.  
Health Canada. An advisory committee statement: National Advisory Committee on Immunization: prevention of pertussis in adolescents and adults. Canada communicable disease report 2003;29:ACS5-6.  
Furlan AD, et al. Massage for low-back pain. *Cochrane DB Syst Rev* 2008;Issue 4.  
Gilbert DN, et al. The Sanford guide to antimicrobial therapy, 39th ed. Sperryville: Antimicrobial Therapy, 2009.  
Gupta BP, et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction. *Arch Intern Med* 2011;171:1797-1803.  
Health Canada. Natural health products directorate 2004 (internet). Available from: <http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/>.  
Holbrook AM (Chair: Ontario Musculoskeletal Therapy Review Panel). Ontario treatment guidelines for osteoarthritis, rheumatoid arthritis, and acute, musculoskeletal injury. Toronto: Queen's Printer of Ontario, 2000:13-24.  
Hueston WJ, Mainous AG. Acute bronchitis. *Am Fam Phys* 1998;57:1270-1279.  
Hunt P. Motivating Change. *Nursing Standard* 2001;16:45-55.  
Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. *Cochrane DB Syst Rev* 2008;Issue 1  
Leech, et al. Sleep medicine, 3rd ed. 2010 (updated 2011).  
Linde K, et al. Acupuncture for migraine prophylaxis. *Cochrane DB Syst Rev* 2009;Issue 4.  
Linde K, et al. Echinacea for preventing and treating the common cold. *Cochrane DB Syst Rev* 2006;Issue 1.  
Linde K et al. St John's wort for depression. *Cochrane DB Syst Rev* 2005;Issue 2.  
Low DE, et al. A practical guide for the diagnosis and treatment of acute sinusitis. *CMAJ* 1997;156:1S.  
Marshall IIR. Zinc for the common cold. *Cochrane DB Syst Rev* 2006;Issue 3.  
McIsaac WJ, et al. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. *CMAJ* 1998;158:75-83.  
McIsaac WJ, Moineddin R, Ross S. Validation of a decision aid to assist physicians in reducing unnecessary antibiotic drug use for acute cystitis. *Arch Intern Med* 2006;167:2201-2206  
Montgomery L, Scoville C. What is the best way to evaluate acute diarrhea? *J Fam Pract* 2002;51.  
Murphy J, et al. Cervical Screening: a guideline for clinical practice in Ontario. *J Obstet Gynaecol Can* 2012;34:453-458.  
National Institute of Health. Herbs at a glance: black cohosh. National Center for Complementary and Alternative Medicine, 2008. Available from: <http://nccam.nih.gov/health/blackcohosh/ata glance.htm>.  
Osteoporosis Canada. Calcium requirements. 2009. Available from: [http://www.osteoporosis.ca/index.php/ci\\_id/5535/la\\_id/1.htm](http://www.osteoporosis.ca/index.php/ci_id/5535/la_id/1.htm).  
Papaiounou A, et al. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010;182:1864-1873.  
Pampallona S, et al. Combined pharmacotherapy and psychological treatment for depression: a systematic review. *Arch Gen Psychiatry* 2004;61:714-9.  
<http://www.participation.org> Accessed May 27, 2012.  
Rambout L, et al. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ* 2007;177:469-79.  
Ridker PM, et al. Rosuvastatin to prevent vascular event in men and women with elevated c-reactive protein. *NEJM* 2008;359:2195-2207.  
Roelofs PDDM, et al. Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane DB Syst Rev* 2008;Issue 1.  
Rowe T, et al. Canadian consensus guidelines on Human Papillomavirus – SOGC clinical practice guidelines. *JOGC* 2007;29:Supplement 3.  
Rowe T, et al. Menopause and osteoporosis update 2009 – SOGC clinical practice guidelines. *JOGC* 2009;31:Supplement 1.  
Schiller LR. Chronic diarrhea. *Curr Treat Options Gastroenterol* 2005;8:259-266.  
Society of Obstetricians and Gynecologists of Canada. Canadian Consensus Guidelines on Human Papillomavirus. *JOGC* 2007;29(8, suppl 3):S29  
St. Michael's Hospital. Fasting blood tests – diagnostic laboratories.  
<http://www.stmichaelshospital.com/programs/labs/fasting.php> Accessed August 23, 2009.  
Swinson RP, et al. Clinical practice guidelines: management of anxiety disorders. *Can J Psychiatry* 2006;51: Supplement 2.  
Toward Optimized Practice Program. Guideline for assessment to diagnosis of adult insomnia. 2006 (2010 update).  
Toward Optimized Practice Program. Guideline for the diagnosis and management of adult primary insomnia. 2006 (2010 update).  
Toward Optimized Practice Program. Guideline for the diagnosis and management of community acquired pneumonia: adult. 2002 (2008 update).  
Toward Optimized Practice Program. Guideline for the diagnosis and management of acute otitis media. 1999 (2008 update).  
Toward Optimized Practice Program. Guideline for the diagnosis and management of acute pharyngitis. 1999 (2008 update).  
Toward Optimized Practice Program. Guideline for the management of acute bronchitis. 2000 (2008 update).  
Toward Optimized Practice Program. Guideline for the treatment of Helicobacter pylori infection in adults. 2000 (2009 update).  
Toward Optimized Practice Program. Guideline for the management of low back pain. 2009 (2011 update).  
Toward Optimized Practice Program. Use of PSA and the early diagnosis of prostate cancer. 2006 (2009 update).  
Towheed T, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane DB Syst Rev* 2005;Issue 2.  
Walsh PC, et al. Campbell's Urology, 8th ed. Philadelphia: WB Saunders, 1998.  
Wong T, Latham-Carmanico C. Canadian guidelines on sexually transmitted infections. Ottawa: Public Health Agency of Canada 2006 (reviewed 2008).  
Wren BG. The benefits of oestrogen following menopause: why hormone replacement therapy should be offered to postmenopausal women. *Med J Aust* 2009;190:321-325.  
Zink T, Chaffin J. Herbal "health" products: what family physicians need to know. *Am Fam Phys* 1998;58:1133-1140.



Ian Brasg and Ahmad Zaheen, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Gabor Kandel, Dr. Piero Tartaro, and Dr. Elaine Yong, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	Upper Gastrointestinal Bleeding	
<b>Anatomy Review</b> . . . . .	<b>2</b>	Approach to Iron Deficiency Anemia	
Overview of Gastrointestinal Tract		Esophageal Varices	
<b>Visualizing the GI Tract</b> . . . . .	<b>3</b>	Mallory-Weiss Tear	
<b>Differential Diagnosis of Common Presenting Complaints</b> . . . . .	<b>4</b>	Lower Gastrointestinal Bleeding	
Nausea/Vomiting		Colorectal Carcinoma (CRC)	
Dysphagia		Colorectal Polyps	
Odynophagia		Familial Colon Cancer Syndromes	
Abdominal Distention		Benign Anorectal Disease	
Acute Abdominal Pain			
Chronic/Recurrent Abdominal Pain		<b>Liver</b> . . . . .	<b>28</b>
Acute Diarrhea		Investigations of Hepatobiliary Disease	
Chronic Diarrhea		Acute Viral Hepatitis (General)	
Constipation		Hepatitis A Virus (HAV)	
Dyspepsia		Hepatitis B Virus (HBV)	
Upper GI Bleed		Hepatitis C Virus (HCV)	
Lower GI Bleed		Autoimmune Chronic Active Hepatitis	
Jaundice		Drug-Induced Liver Disease	
<b>Esophagus</b> . . . . .	<b>6</b>	Wilson's Disease	
Gastroesophageal Reflux Disease (GERD)		Hemochromatosis	
Barrett's Esophagus		Alcoholic Liver Disease	
Eosinophilic Esophagitis		Non-Alcoholic Fatty Liver Disease (NAFLD)	
Dysphagia		Acute Liver Failure (ALF; Formerly Fulminant Hepatic Failure)	
Esophageal Motor Disorders		Cirrhosis	
Esophageal Diverticula		Hepatocellular Carcinoma (HCC)	
Peptic Stricture (from Esophagitis)		(see <a href="#">General Surgery</a> , GS43)	
Esophageal Carcinoma (see <a href="#">General Surgery</a> , GS14)		Liver Transplantation (see <a href="#">General Surgery</a> , GS44)	
Webs and Rings		Portal Hypertension	
Infectious Esophagitis		Hepatic Encephalopathy	
<b>Stomach and Duodenum</b> . . . . .	<b>10</b>	Ascites	
Dyspepsia		<b>Biliary Tract</b> . . . . .	<b>40</b>
Gastric Acid Secretion		Jaundice	
Gastritis		Gilbert's Syndrome	
Peptic Ulcer Disease (PUD)		Sclerosing Cholangitis	
<i>H. pylori</i> -Induced Peptic Ulceration		Primary Biliary Cirrhosis (PBC)	
NSAID-Induced Ulceration		Secondary Biliary Cirrhosis	
Stress-Induced Ulceration		Biliary Colic, Cholecystitis (see <a href="#">General Surgery</a> , GS46)	
Gastric Carcinoma (see <a href="#">General Surgery</a> , GS18)		Ascending Cholangitis	
<b>Small and Large Bowel</b> . . . . .	<b>15</b>	<b>Pancreas</b> . . . . .	<b>44</b>
Classification of Diarrhea		Pancreatic Enzyme Abnormalities	
Acute Diarrhea		Acute Pancreatitis	
Traveller's Diarrhea		Chronic Pancreatitis	
(see <a href="#">Infectious Diseases</a> , ID14)		Autoimmune Pancreatitis	
Chronic Diarrhea		<b>Clinical Nutrition</b> . . . . .	<b>47</b>
Maldigestion and Malabsorption		Determination of Nutritional Status	
Celiac Disease (Gluten Enteropathy/Sprue)		Enteral Nutrition (EN)	
Inflammatory Bowel Disease (IBD)		Parenteral Nutrition (PN)	
Crohn's Disease (CD)		<b>Common Medications</b> . . . . .	<b>49</b>
Ulcerative Colitis (UC)		<b>Landmark Gastroenterology Trials</b> . . . . .	<b>51</b>
Irritable Bowel Syndrome (IBS)		<b>References</b> . . . . .	<b>51</b>
Constipation			

## Acronyms

ALF	acute liver failure
BE	Barrett's esophagus
BT	biologic therapy
CCK	cholecystokinin
CD	Crohn's disease
DES	diffuse esophageal spasm
EIM	extraintestinal manifestation
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound
EVL	endoscopic variceal ligation
FAP	familial adenomatous polyposis
GE	gastroesophageal
GERD	gastroesophageal reflux disease
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HNPCC	hereditary non-polyposis colorectal cancer
HRS	hepatorenal syndrome
HVPG	hepatic venous pressure gradient
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
INH	isoniazid
MRCP	magnetic resonance cholangiopancreatography
NAC	N-acetylcysteine
NAFLD	non-alcoholic fatty liver disease
NERD	non-erosive reflux disease
NMS	neuroleptic malignant syndrome
OGD	oesophagogastroduodenoscopy
PBC	primary biliary cirrhosis
PPI	proton pump inhibitor
PSC	primary sclerosing cholangitis
PTC	percutaneous transhepatic cholangiography
PUD	peptic ulcer disease
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt
UC	ulcerative colitis

## Anatomy Review

### Overview of Gastrointestinal Tract

- the gastrointestinal tract runs from mouth to anus ("gum to bum")

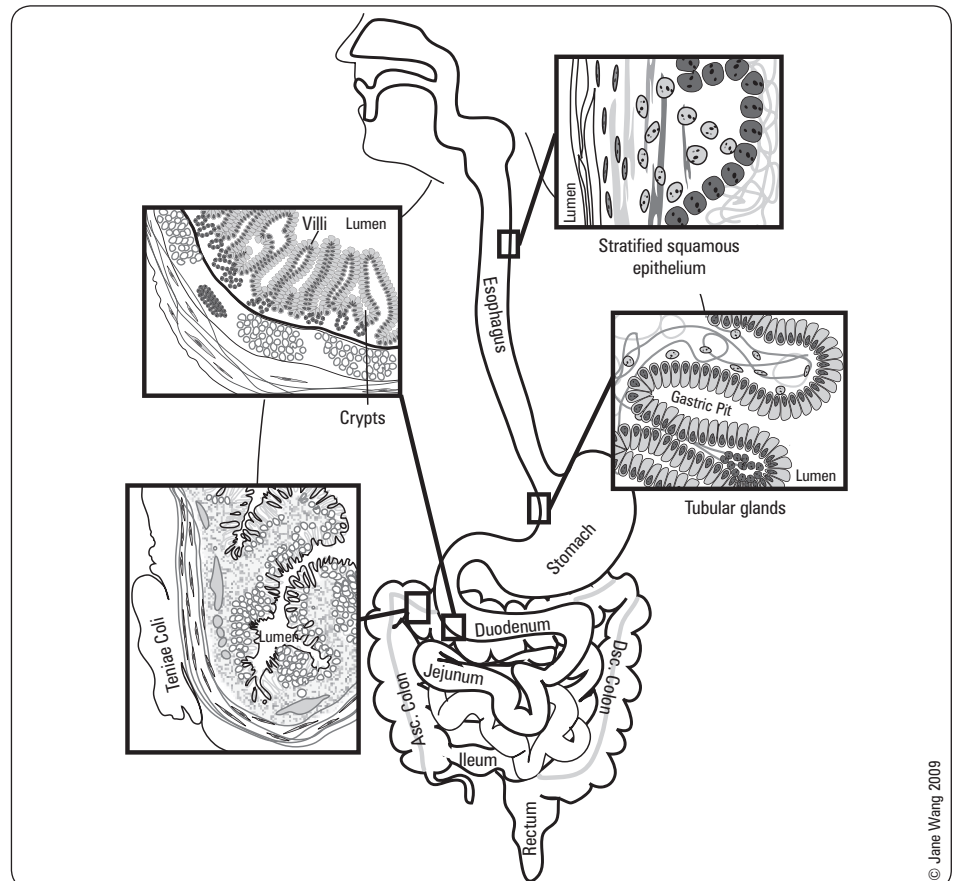


Figure 1. Overview of gastrointestinal tract

Table 1. Summary of Gastrointestinal Tract Structure and Function

Organ	Function	Blood Supply	Innervation	Histology and Structural Features
<b>Esophagus</b>	<ul style="list-style-type: none"> <li>Muscular tube approximately 25 cm long with a diameter of 2 cm</li> <li>Extends from pharynx to the stomach</li> </ul>	<ul style="list-style-type: none"> <li>Arterial: left gastric artery and left inferior phrenic artery</li> <li>Venous: <ul style="list-style-type: none"> <li>Left gastric vein → portal venous system</li> <li>Esophageal veins → azygos vein → IVC (systemic)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks)</li> <li>Sympathetic innervation via thoracic trunks of the greater splanchnic nerves</li> </ul>	<ul style="list-style-type: none"> <li>Mucosa: stratified squamous epithelium</li> <li>Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells</li> <li>Muscularis propria (muscularis externa): inner circular, outer longitudinal muscle <ul style="list-style-type: none"> <li>Upper 1/3: striated muscle</li> <li>Middle 1/3: transition zone</li> <li>Lower 1/3: smooth muscle</li> </ul> </li> </ul>
<b>Stomach</b>	<ul style="list-style-type: none"> <li>Delivers food to intestine for digestion and absorption</li> <li>Secretes acid, probably to reduce enteric infections/pneumonia; facilitate digestion of protein/iron/B<sub>12</sub></li> <li>Secretes intrinsic factor to facilitate B<sub>12</sub> absorption</li> <li>Minor contribution to initial protein digestion via pepsin</li> </ul>	<ul style="list-style-type: none"> <li>Lesser curvature: <ul style="list-style-type: none"> <li>Right and left gastric arteries (from celiac trunk)</li> </ul> </li> <li>Greater curvature: <ul style="list-style-type: none"> <li>Right and left gastromental (gastroepiploic) arteries (from gastroduodenal and splenic a. respectively)</li> </ul> </li> <li>Fundus: short and posterior gastric arteries (from the splenic artery)</li> </ul>	<ul style="list-style-type: none"> <li>Parasympathetic innervation via vagus nerve</li> <li>Sympathetic innervation via celiac plexus (from T6-T9)</li> </ul>	<ul style="list-style-type: none"> <li>5 parts: <ul style="list-style-type: none"> <li>Cardia</li> <li>Fundus</li> <li>Body</li> <li>Antrum</li> <li>Pylorus</li> </ul> </li> </ul>
<b>Duodenum</b>	<ul style="list-style-type: none"> <li>Modulates enteral pH via secretin → decreased gastric acid secretion, increased bicarbonate secretion</li> <li>Secretes cholecystokinin (CCK) to stimulate bile secretion</li> <li>Site of iron absorption</li> </ul>	<ul style="list-style-type: none"> <li>Branches of celiac artery and superior mesenteric artery (SMA)</li> </ul>	<ul style="list-style-type: none"> <li>Parasympathetic innervation via vagus nerve</li> <li>Sympathetic innervation via greater and lesser splanchnic nerves</li> </ul>	<ul style="list-style-type: none"> <li>4 parts <ul style="list-style-type: none"> <li>Superior (5 cm)</li> <li>Descending (7-10 cm)</li> <li>Horizontal (6-8 cm)</li> <li>Ascending (5 cm)</li> </ul> </li> <li>1st part is intraperitoneal; rest is retroperitoneal</li> </ul>

**Table 1. Summary of Gastrointestinal Tract Structure and Function** (continued)

Organ	Function	Blood Supply	Innervation	Histology and Structural Features
<b>Jejunum</b>	<ul style="list-style-type: none"> <li>Absorption of salt, water and nutrients (protein, carbohydrates, fat, folic acid, and vit A, B, C, D, E, K)</li> </ul>	<ul style="list-style-type: none"> <li>Superior mesenteric artery</li> </ul>	<ul style="list-style-type: none"> <li>Parasympathetic innervation via fibers of the posterior vagal trunk</li> <li>Sympathetic innervation via fibers of T8-T10</li> </ul>	<ul style="list-style-type: none"> <li>Deep red colour</li> <li>2-4 cm in thickness</li> <li>Has a thick and heavy wall</li> <li>Plicae circulares are large, tall and closely packed</li> <li>Has long vasa recta</li> <li>Scant fat in mesentery</li> <li>Scant Peyer's patches</li> </ul>
<b>Ileum</b>	<ul style="list-style-type: none"> <li>Absorption of salt, water, nutrients, soluble vitamins (only site of vit B<sub>12</sub> absorption) and bile salt (entero-hepatic circulation)</li> </ul>	<ul style="list-style-type: none"> <li>Superior mesenteric artery</li> </ul>	<ul style="list-style-type: none"> <li>Same as jejunum</li> </ul>	<p>When compared to jejunum:</p> <ul style="list-style-type: none"> <li>Paler pink colour</li> <li>2-3 cm in thickness</li> <li>Has a thin and light wall</li> <li>Plicae circulares are small and sparse</li> <li>Contains more fat in mesentery than jejunum</li> <li>Has many Peyer's patches</li> </ul>
<b>Large Bowel</b>	<ul style="list-style-type: none"> <li>Absorption of water (5-10% of total water)</li> <li>Bacteria: further digestion of chyme and metabolism of undigested CHO to short chain fatty acids</li> <li>Formation and storage of feces</li> </ul>	<ul style="list-style-type: none"> <li>Branches of superior and inferior mesenteric arteries</li> <li>Rectal blood supply: sigmoid, right pudendal and rectal arteries</li> </ul>	<ul style="list-style-type: none"> <li>Parasympathetic innervation via vagus nerve</li> <li>Sympathetic innervation via greater and lesser splanchnic nerves</li> </ul>	<ul style="list-style-type: none"> <li>Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal</li> <li>Features include teniae coli, haustra, and omental appendices</li> </ul>
<b>Liver</b>	<ul style="list-style-type: none"> <li>Glucose homeostasis</li> <li>Plasma protein synthesis</li> <li>Lipid and lipoprotein synthesis</li> <li>Bile acid synthesis and secretion</li> <li>Vitamin A, D, E, K, B<sub>12</sub> storage</li> <li>Biotransformation, detoxification</li> <li>Excretion of compounds</li> </ul>	<ul style="list-style-type: none"> <li>2 sources               <ul style="list-style-type: none"> <li>Portal vein (75-80%)</li> <li>Hepatic artery (20-25%)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Sympathetic innervation via fibers of the celiac plexus</li> <li>Parasympathetic innervation via fibers of the anterior and posterior vagal trunks</li> </ul>	<ul style="list-style-type: none"> <li>Largest internal organ</li> <li>Composed of 4 lobes (left, right, caudate, quadrate) and divided into 8 segments</li> </ul>
<b>Biliary Tract</b>	<ul style="list-style-type: none"> <li>Gallbladder functions to store and release bile that is produced in the liver</li> <li>Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids and bilirubin</li> <li>CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release</li> </ul>	<ul style="list-style-type: none"> <li>Cystic artery</li> </ul>	<ul style="list-style-type: none"> <li>Parasympathetic innervation via vagus nerve</li> <li>Sympathetic and visceral innervation via celiac nerve plexus</li> <li>Somatic afferent fibers via right phrenic nerve</li> </ul>	<ul style="list-style-type: none"> <li>Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct and ampulla of Vater</li> </ul>
<b>Pancreas</b>	<ul style="list-style-type: none"> <li>Endocrine function: islets of Langerhans produce glucagon, insulin and somatostatin (from the <math>\alpha</math>, <math>\beta</math> and <math>\delta</math> cells, respectively)</li> <li>Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin and carboxypeptidase</li> </ul>	<ul style="list-style-type: none"> <li>Anterior superior pancreaticoduodenal artery (from the celiac trunk)</li> <li>Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery)</li> <li>Dorsal pancreatic artery (from the splenic artery)</li> <li>Pancreatic veins drain into the portal, splenic and superior mesenteric veins</li> </ul>	<ul style="list-style-type: none"> <li>Parasympathetic innervation via vagus nerve</li> <li>Sympathetic innervation via abdominopelvic splanchnic nerves</li> </ul>	<ul style="list-style-type: none"> <li>4 parts of pancreas: head (includes uncinate process), neck, body, and tail</li> <li>(Major) Pancreatic duct connecting to common bile duct prior to ampulla of Vater</li> <li>Accessory pancreatic duct connecting directly to duodenum</li> </ul>

## Visualizing the GI Tract

- see also [Medical Imaging](#), MI10



### Esophagus, Stomach, Duodenum

- oesophagogastrroduodenoscopy (OGD): best visualization of mucosa; also allows for therapeutic intervention (banding varices, cauterizing/clipping/injecting bleeding ulcers, and dilating esophageal strictures)
  - consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation)
  - endotracheal intubation first if massive upper GI bleed, acidosis or unable to protect airway



#### Retroperitoneal Structures

##### SAD PUCKER

Suprarenal glands (adrenal glands)  
 Aorta/IVC  
 Duodenum (second to fourth segments)  
 Pancreas (tail is intraperitoneal)  
 Ureters  
 Colon (only the ascending and descending branches)  
 Kidneys  
 Esophagus  
 Rectum



Only the ileum (not jejunum), can absorb vitamin B<sub>12</sub> and bile acids.

### Small Bowel

- most difficult to visualize, especially if mucosal detail is needed
- CT enterography more accurate than small bowel follow through, but both have low sensitivity
- MRI enteroclysis increasingly available (use enteroclysis if dilation of the small bowel might improve sensitivity, such as diverticulosis, or if stricture suspected)
- “double balloon” enteroscopy (enteroscope with balloons proximally and distally to propel endoscope into jejunum from mouth or into ileum from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction) is also accurate in diagnosis but unable to provide any therapeutic intervention

### Colon and Terminal Ileum

- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis and severe colitis (increased risk of perforation)
- CT colonoscopy (“virtual colonoscopy”) more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon) and fistulae; increasing evidence for use in colorectal cancer screening

### Pancreatic/Biliary Duct

- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if endoscopic draining necessary, strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required

## Differential Diagnosis of Common Presenting Complaints



Table 2. Differential Diagnosis of Common Presenting Complaints

NAUSEA/ VOMITING	With Abdominal Pain		Without Abdominal Pain	
	Relieved by Vomiting	Not Relieved by Vomiting	Headache/Dizziness	No other Symptoms
	Gastric outlet obstruction Small bowel obstruction GERD (regurgitation more common)	Gallbladder disease Pancreatitis Myocardial infarction Hepatitis Infectious gastroenteritis	Cerebral tumour Migraine Vestibular disease Increased ICP	Drugs Uremia Pregnancy Metabolic (e.g. hypercalcemia) Gastroparesis (e.g. diabetes) Ketoacidosis
DYSPHAGIA	Mechanical (Solids)	Motility (Solids and Liquids)	Other	
	Peptic stricture/cancer Eosinophilic esophagitis Extrinsic compression Schatzki ring/esophageal web Zenker's diverticulum	Achalasia Diffuse esophageal spasm Scleroderma	Foreign Body Eosinophilic esophagitis	
ODYNOPHAGIA	Infection	Inflammation/Ulceration	Drugs	Other
	Candida Herpes CMV (common only in those who are immunosuppressed)	Caustic damage Eosinophilic esophagitis	Quinidine Iron Vitamin C Antibiotics (e.g. tetracycline) Bisphosphonates	Radiation
ABDOMINAL DISTENTION	Fluid (Ascites)		Flatulence	Other
	Portal HTN	Normal Portal Pressure		
	Cirrhosis Cardiac failure Hepatic vein thrombosis	Cancer (esp. ovarian) Pancreatitis TB	Functional bowel disease (e.g. IBS) Fibre Lactose intolerance Chewing gum (e.g. sorbitol, mannitol)	Constipation Colonic obstruction Dysmotility Pregnancy (fetus) Obesity (fat) Blood Large tumours (fatal growth)



#### Commonly Forgotten Causes of Vomiting

- Drugs
- Uremia
- CNS Disease
- Pregnancy



#### Differential Diagnosis of Abdominal Distention

- 6 Fs**  
 Fat  
 Feeces  
 Fetus  
 Flatus  
 Fluid  
 Fatal Growth



#### Acute Upper Abdominal Pain

Remember to rule out thoracic sources, e.g. myocardial infarction, pneumonia, dissecting aneurysm.

Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

ACUTE ABDOMINAL PAIN	Upper/Mid-Abdomen	Lower Abdomen			
	Gastroenteritis Cholecystitis Perforated peptic ulcer Pancreatitis Small bowel obstruction Mesenteric ischemia Ruptured aortic aneurysm	Gastroenteritis Appendicitis Diverticulitis Crohn's disease Pelvic inflammatory disease Ectopic pregnancy			
CHRONIC/RECURRENT ABDOMINAL PAIN	Inflammatory	Neoplastic/Vascular	Toxin	Other	
	PUD Biliary colic IBD Chronic pancreatitis	Recurrent bowel obstruction Mesenteric ischemia Sickle cell anemia	Lead poisoning	Mittelschmerz Endometriosis Porphyria IBS Radiculopathy Abdominal wall pain syndrome	
ACUTE DIARRHEA	Inflammatory		Non-Inflammatory		
*Causes of bloody diarrhea	<b>Bacterial</b> <i>Shigella</i> * <i>Salmonella</i> * <i>Campylobacter</i> * <i>Yersinia</i> * <i>E. coli</i> (EHEC O157:H7)* <i>C. difficile</i>	<b>Protozoal</b> <i>E. histolytica</i> * (amebiasis) Strongyloides <b>Others</b> NSAIDs IBD* Ischemic*	<b>Bacterial</b> <i>S. aureus</i> <i>C. perfringens</i> <i>B. cereus</i> <i>E. coli</i> (ETEC, EPEC) <i>Salmonella enteritidis</i> <i>Vibrio cholera</i> <b>Protozoal</b> <i>Giardia lamblia</i>	<b>Viral</b> Rotavirus Norwalk CMV <b>Drugs</b> Antibiotics Colchicine Laxatives Antacids (magnesium)	
CHRONIC DIARRHEA	(a) Organic				(b) Functional
	Inflammatory	Secretory	Steatorrheic	Osmotic	
	IBD Infectious ( <i>C. difficile</i> , TB, CMV, HSV) Ischemic bowel Radiation colitis Neoplasia	Stimulant laxatives Post-ileal resection/cholecystectomy (bile salts) Bacterial toxins Vasculitis Neoplasia (Colon Ca, Carcinoid, VIPoma) Addison's disease Congenital syndromes	<i>Giardia lamblia</i> Celiac sprue Chronic pancreatitis Chronic cholestasis	Osmotic laxatives Lactose intolerance Chewing gum (sorbitol, mannitol)	IBS Constipation (overflow diarrhea) Anal sphincter dysfunction
CONSTIPATION: if no associated rectal bleeding/weight loss, etc., usually no cause found					
	Colorectal cancer Stricture Extrinsic compression Anal disease Rectocele	Medications (narcotics, antidepressants, calcium channel blockers) Metabolic (diabetes, thyroid, hypercalcemia)	Neurological (Parkinson's, multiple sclerosis, stroke) Collagen vascular disease (scleroderma, dermatomyositis)		
DYSPEPSIA	Common	Uncommon	Rare		
	Functional dyspepsia Drug side effect Peptic ulcer GERD	Angina Crohn's disease Cancer Gallstones Aerophagia	<i>Giardia lamblia</i> Malabsorption (celiac sprue)		
UPPER GI BLEED	Common	Uncommon	Rare		
	Ulcers ( <i>H. pylori</i> , ASA, NSAIDs) Esophageal varices Mallory-Weiss tears Erosive esophagitis Erosive gastritis	Tumours Arteriovenous malformation Dieulafoy's lesion Gastric antral vascular ectasia Portal hypertensive gastropathy	Aorto-enteric fistulas Hemobilia		
LOWER GI BLEED	Common	Uncommon	Rare		
	Diverticulosis Ischemia Angiodysplasia (elderly) Infectious Anorectal (hemorrhoids, fissure, ulcer)	Upper GI bleed (brisk) Post-polypectomy Radiation colitis IBD	Intussusception Vasculitides Stercoral ulcer Coagulopathies		



#### Obscure But Treatable Causes of Abdominal Pain

- Porphyria
- Angioedema
- Familial Mediterranean Fever
- Vasculitis (e.g. polyarteritis nodosa)



Rule out IBD when patient presents with bloody diarrhea.

**Table 2. Differential Diagnosis of Common Presenting Complaints** (continued)

JAUNDICE (UNCONJUGATED BILIRUBIN)	Overproduction	Decreased Hepatic Intake	Decreased Conjugation
	Hemolysis Ineffective erythropoiesis (e.g. megaloblastic anemias)	Gilbert's syndrome Drugs (e.g. rifampin)	Drug inhibition (e.g. chloramphenicol) Crigler-Najjar syndromes type I and II Gilbert's syndrome Neonatal jaundice
JAUNDICE (CONJUGATED BILIRUBIN)	Impaired Hepatic Secretion		Extrahepatic Biliary Obstruction
	<b>Hepatocellular disease – by far the most common</b> Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy) Drug-induced cholestasis (e.g. oral contraceptives, chlorpromazine) Primary biliary cirrhosis (PBC) Primary sclerosing cholangitis (PSC) Sepsis Post-operative		<b>Intraductal obstruction:</b> Gallstones Biliary stricture Parasites Malignancy (cholangiocarcinoma) Sclerosing cholangitis <b>Extraductal obstruction:</b> Malignancy (e.g. pancreatic cancer, lymphoma) Metastases in peri-portal nodes <b>Inflammation (e.g. pancreatitis)</b>

## Esophagus

### Gastroesophageal Reflux Disease (GERD)

#### Definition

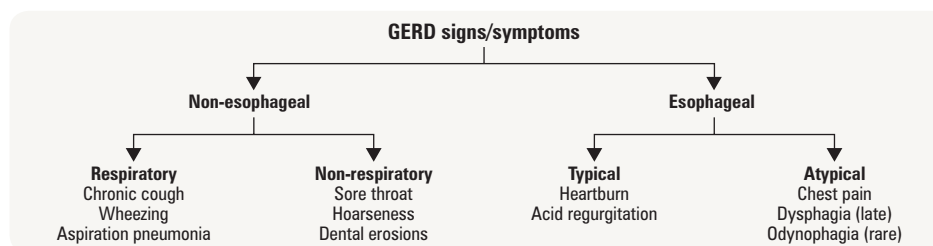
- condition in which the stomach contents (solid or liquid) leak backwards from the stomach into the esophagus (the tube from the mouth to the stomach)

#### Etiology

- inappropriate transient relaxations of lower esophageal sphincter (LES) – most common
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, increased intra-abdominal pressure
- acid hypersecretion (rare): Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see [General Surgery](#), GS22)

#### Clinical Features

- “heartburn” (pyrosis) and acid regurgitation (together are 80% sensitive and specific for reflux) ± sour regurgitation, water brash, sensation of a lump in the throat (bolus sensation) and frequent belching
- non-esophageal symptoms (see below) are increasingly recognized of being poor predictors of reflux

**Figure 2. Signs and symptoms of GERD**

#### Investigations

- usually a clinical diagnosis based on symptom history and relief following a trial of pharmacotherapy (proton pump inhibitor (PPI): symptom relief 80% sensitive for reflux)
- gastroscopy indications (*Ann Intern Med* 2012;157:808-816):
  - absolute indications:
    - heartburn accompanied by red-flags (bleeding, weight loss, etc.)
    - persistent reflux symptoms or previous severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI 2x daily
    - history of esophageal stricture with persistent dysphagia
- repeat endoscopy indicated only if known Barrett's (or recurrence of symptoms) because future likelihood of Barrett's and esophagitis is minimal if the first endoscopy is normal



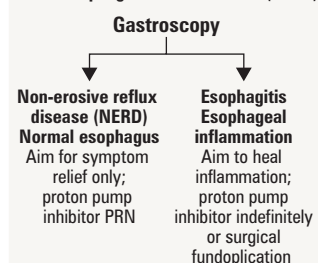
**Epigastric discomfort** = postprandial fullness, early satiety, epigastric pain or burning.



#### Foods/Substances that Aggravate GERD Symptoms

- EtOH
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices

#### Gastroesophageal Reflux Disease (GERD)

**Figure 3. Classification and gastroscopic findings of GERD**

Esophageal damage from reflux is most severe at first gastroscopy, therefore necessary only once for patients with NERD.



- esophageal manometry (study of esophageal motility)
  - may be done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure esophagus functional
  - surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to be successful if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- 24-h pH monitoring: most accurate test, but rarely required or performed
  - most useful if PPIs do not improve symptoms

### Management

- PPIs are the most effective therapy and usually need to be continued as maintenance therapy
- on-demand: antacids ( $\text{Mg}(\text{OH})_2$ ,  $\text{Al}(\text{OH})_3$ , alginate),  $\text{H}_2$ -blockers or PPIs can be used for NERD
- diet helps symptoms, not the disease; avoid alcohol, coffee, spices, tomatoes and citrus juices
- only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)
- dyspepsia may recur if therapy is discontinued

### Complications

- esophageal stricture disease – scarring can lead to dysphagia (solids)
- ulcer
- bleeding
- Barrett's esophagus (see below) and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

## Barrett's Esophagus

### Definition

- metaplasia of normal squamous esophageal epithelium to abnormal columnar epithelium containing intestinal metaplasia

### Etiology

- thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

### Epidemiology

- in North America and Western Europe, 0.5-2.0% of adults are thought to have Barrett's esophagus
- up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- more common in males, age >50, Caucasians, smokers, overweight, hiatus hernia and long history of reflux symptoms

### Pathophysiology

- endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes to premalignant changes in abnormal columnar epithelium, characterized as low- or high-grade dysplasia

### Significance

- rate of malignant transformation is approximately 0.12% per year for all BE patients prior to dysplasia
- risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance
- increased gastric acid secretion is more frequently associated with Barrett's esophagus as opposed to reflux alone

### Management

- acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication)
- endoscopy every 3 yr if no dysplasia
- high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes; however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation
- if low grade dysplasia, both surveillance and endoscopic ablation/resection are satisfactory options



Up to 25% of patients with Barrett's esophagus do not report symptoms of GERD.



**Updated Guidelines 2008 for the Diagnosis, Surveillance and Therapy of Barrett's Esophagus**  
*Am J Gastroenterol* 2008;103:788-797

- **Screening** of the general population is not recommended and needs to be individualized based on risk factors. Role of esophageal capsule endoscopy for screening is currently under investigation.
- **Surveillance** interval is based on grade of dysplasia. If no dysplasia confirmed on two endoscopies within the year, then q3y. For low grade dysplasia (LGD), repeat endoscopy within 6 mo to ensure there is no high grade dysplasia (HGD) and if none, then q1y until no dysplasia on two consecutive endoscopies. If HGD, repeat endoscopy within 3 mo to ensure there is no adenocarcinoma and recommend intervention (endoscopic resection) or intensive surveillance (endoscopy q3m).
- **Diagnosis** using alternative imaging techniques (fiberoptic, chromoendoscopy) and biomarkers (DNA content abnormalities, loss of heterozygosity or methylation of specific genes) are being investigated but none are currently ready for routine clinical use.
- **Treatment** of reflux symptoms with PPI decreases the development of dysplasia. Surgery (fundoplication) for patients without major co-morbidities and whose reflux symptoms are controlled on PPI has a 20% failure rate at 5 yr and has not shown to decrease progression to adenocarcinoma.
- **Prognosis**: 5 yr risk of esophageal adenocarcinoma in high grade dysplasia is >30%.
- **Management** in high grade dysplasia, surveillance with intensive biopsy, endoscopic ablation, or esophagectomy produce similar outcomes and thus should be individualized to patient preference and local expertise.

## Eosinophilic Esophagitis

### Definition

- inflammatory condition with prominence of eosinophils on esophageal biopsy
- most commonly found in children, but increasingly recognized in adults

### Etiology

- unknown; may be an “allergic” disorder in children
- cytokines cause edema and fibrosis

### Clinical Features

- odynophagia or dysphagia (solids); history often dates back to childhood
- first presentation may be to ER with food bolus impaction
- allergies common

### Investigations

- endoscopy may reveal multiple rings or “crepe-paper” appearance
- biopsy showing increased eosinophils is necessary to confirm diagnosis

### Management

- corticosteroid (e.g. fluticasone) spray (swallowed not inhaled)
- budesonide in a matrix to increase contact time with esophageal mucosa
- leukotriene B4 inhibitors (e.g. Montelukast)
- rule out food allergies: elimination diets have been an effective therapy in children

### Complications

- increased risk of perforation with endoscopic dilatation procedures

## Dysphagia

### Definition

- difficulty swallowing, sensation of food “sticking” after swallowing

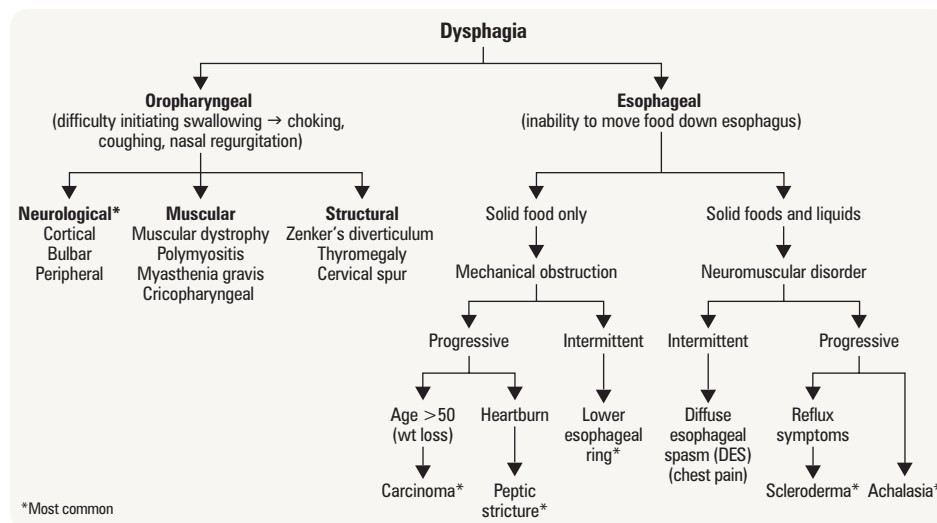


Figure 4. Approach to dysphagia (eosinophilic esophagitis omitted)



### Key Questions in Dysphagia

- Difficulty in starting swallowing?
- Associated symptoms? (regurgitation, change in voice pitch, weight loss)
- Solids, liquids or both?
- Intermittent or progressive?
- History of heartburn?
- Change in eating habits/diet?



Dysphagia = Difficulty in swallowing  
Odynophagia = Pain on swallowing



## Esophageal Motor Disorders

### Symptoms

- dysphagia with solids and liquids
- chest pain (in some disorders)


### Diagnosis

- motility study (esophageal manometry)
- barium swallow sometimes helpful

### Causes (Table 3)

- idiopathic
- achalasia (painless)
- scleroderma (painless)
- diabetes
- diffuse esophageal spasm (DES): rare and can be difficult to diagnose due to intermittent presentation

Table 3. Esophageal Motor Disorders

Disorder	Achalasia	Scleroderma	Diffuse Esophageal Spasm (DES)
<b>Definition</b>	<ul style="list-style-type: none"> <li>Failure of smooth muscle relaxation at LES</li> <li>Progressive loss of peristaltic function</li> </ul>	<ul style="list-style-type: none"> <li>See <a href="#">Rheumatology</a>, RH13</li> <li>Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening)</li> </ul>	<ul style="list-style-type: none"> <li>Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)</li> </ul>
<b>Etiology</b>	<ul style="list-style-type: none"> <li>Usually idiopathic</li> <li>2° or pseudo-achalasia: e.g. malignancy, Chagas disease (<i>Trypanosoma cruzi</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Involves autoimmune, genetic, hormonal, and environmental factors</li> <li>Dysphagia: caused by reflux, dysmotility, or both</li> </ul>	<ul style="list-style-type: none"> <li>Idiopathic</li> </ul>
<b>Pathophysiology</b>	<ul style="list-style-type: none"> <li>Inflammatory degeneration of Auerbach's plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis</li> </ul>	<ul style="list-style-type: none"> <li>Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia</li> </ul>	<ul style="list-style-type: none"> <li>Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis</li> </ul>
<b>Diagnosis</b>	 <ul style="list-style-type: none"> <li>CXR: no air in stomach, dilated esophagus</li> <li>Barium studies: esophagus terminates in narrowing at LES ("bird's beak")</li> <li>Endoscopy: r/o malignancy</li> <li>Manometry: definitive diagnosis (signs listed above)</li> </ul>	<ul style="list-style-type: none"> <li>Clinical features of scleroderma</li> <li>Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus</li> </ul>	<ul style="list-style-type: none"> <li>Barium x-ray: "Corkscrew pattern"</li> <li>Manometry: &gt;30% (but &lt;100%) of esophageal contractions are aperistaltic</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>Dilatation of LES with balloon, ± GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%)</li> <li>Injection of botulinum toxin into LES (temporary)</li> <li>Surgery (myomectomy)</li> </ul>	<ul style="list-style-type: none"> <li>Medical: aggressive GERD therapy (PPIs bid)</li> <li>Surgery: anti-reflux surgery (gastroplasty, last resort)</li> </ul>	<ul style="list-style-type: none"> <li>Reassurance not cardiac pain</li> <li>Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit</li> <li>Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful); balloon dilatation</li> </ul>

## Esophageal Diverticula

### Definition

- outpouchings of one or more layers of the esophageal tract

### Clinical Features

- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

### Classification

- classified according to location
  - pharyngoesophageal (Zenker's) diverticulum
    - most frequent form of esophageal diverticulum
    - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
    - symptoms: dysphagia, regurgitation of undigested food, halitosis
    - treatment: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac
  - mid-esophageal diverticulum
    - secondary to mediastinal inflammation, motor disorders
    - usually asymptomatic; no treatment required
  - just proximal to LES (pulsatile type)
    - usually associated with motor disorders
    - usually asymptomatic; no treatment required

## Peptic Stricture (from Esophagitis)

- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

### Treatment

- endoscopic dilatation and indefinite PPI
- anti-reflux surgery if above treatment unsuccessful

## Esophageal Carcinoma

- see [General Surgery](#), GS14



## Webs and Rings

- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

### Clinical Features

- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Plummer-Vinson (or Patterson-Kelly syndrome)
  - upper esophageal web with iron deficiency, plus cheilosis (dry scaling and fissuring of the lips) and koilonychia (concave outer nail surface)
  - usually in middle-aged females (>40 yr)
  - elevated risk of hypopharyngeal carcinoma
- Schatzki's ring
  - mucosal ring at squamo-columnar junction above a hiatus hernia
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic bougie



#### Plummer-Vinson Syndrome Triad

- Fe Deficiency anemia
- Dysphagia
- Esophageal webs

## Infectious Esophagitis

### Definition

- severe mucosal inflammation and ulceration as a result of a viral or a fungal infection

### Risk Factors

- diabetes
- chemotherapeutic agents
- immunocompromised states

### Symptoms

- characteristically odynophagia, less often dysphagia
- diagnosis is via endoscopic visualization and biopsy

### Appearance

- *Candida* (most common): whitish-yellow plaques without visible ulceration or inflammation
- Herpes (second most common), CMV: focal ulcers

### Treatment

- *Candida*: nystatin swish and swallow, ketoconazole, fluconazole
- Herpes: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV ganciclovir, famciclovir or oral valganciclovir



#### Red Flags of Dyspepsia

(raise suspicion of gastric malignancy):

- Unintended weight loss
- Persistent vomiting
- Progressive dysphagia
- Odynophagia
- Unexplained anemia or iron deficiency
- Hematemesis
- Jaundice
- Palpable abdominal mass or lymphadenopathy
- Family history of upper GI cancer
- Previous gastric surgery

## Stomach and Duodenum



## Dyspepsia

### Definition

- intermittent epigastric discomfort, characteristically develops after eating

### History and Physical

- history: most important are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical examination: adenopathy, abdominal mass/organomegaly, Carnett's sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

### Investigations

- laboratory: usual (CBC, liver enzymes, glucose, Cr, etc.) plus amylase, albumin
- consider trial of empiric anti-secretory drug therapy, non-invasive testing for *H. pylori* infection, endoscopy, barium radiography



The most common cause of dyspepsia is functional (idiopathic) dyspepsia  
"Neither clinical impression nor computer models can adequately distinguish between organic disease and functional disease in patients referred for endoscopic evaluation of dyspepsia."

JAMA 2006;295:1566-1576



#### Key Questions to Ask

- Dysphagia
- Weight Loss

Gastric Acid Secretion

Stomach

- primary function is mechanical grinding of food facilitating early enzymatic digestion into chyme and propulsion into duodenum

Table 4. Cells of the Gastric Mucosa

Cell Type	Secretory Product	Important Notes
Parietal cells	Gastric acid (HCl) Intrinsic factor	Stimulated by histamine, ACh, gastrin
Chief cells	Pepsinogen	Stimulated by vagal input and local acid
G-cells	Gastrin	Stimulates H <sup>+</sup> production from parietal cells
Superficial epithelial cells	Mucus, HCO <sub>3</sub> <sup>-</sup>	Protect gastric mucosa
Neuroendocrine cells	Multiple (e.g. somatostatin, inhibits cell secretion)	Involved in neural, hormonal and paracrine pathways

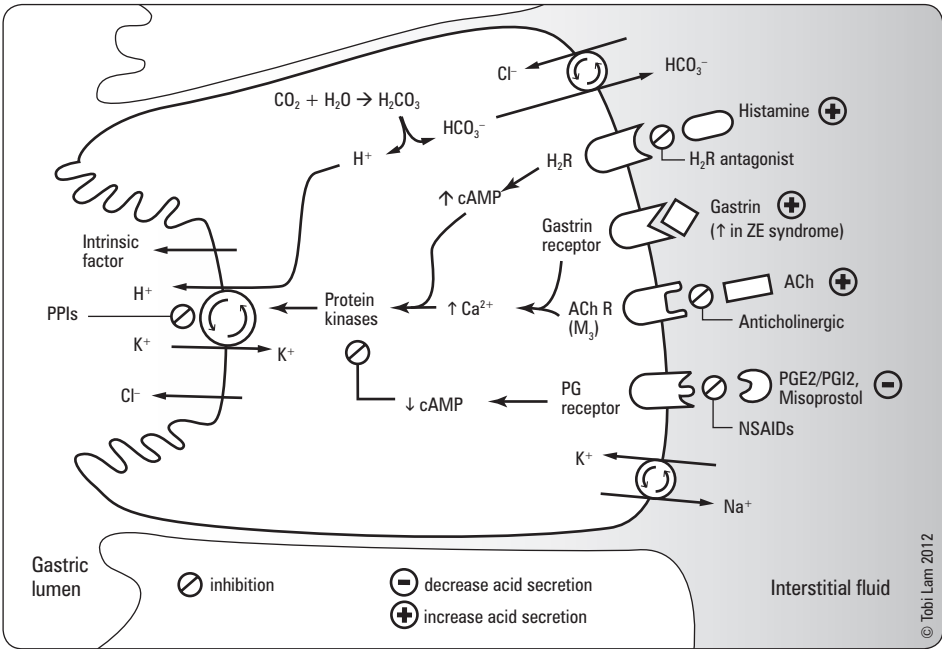


Figure 5. Stimulation of H<sup>+</sup> secretion from the parietal cell

Gastritis

Definition

- defined histologically: inflammation of the stomach mucosa

Etiology

- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

Table 5. Updated Sydney Classification of Gastritis

Type	Common Etiology
<b>Acute Gastritis</b>	
Hemorrhagic/erosive gastritis	Alcohol*, Aspirin®/NSAID*, shock/physiological stress* (seen in ICU patients)
Helicobacter gastritis	Helicobacter pylori*
<b>Chronic Gastritis</b>	
Non-atrophic	Helicobacter pylori*
Atrophic	Helicobacter pylori*, dietary, environmental factors (multi-focal), autoimmunity
Chemical	NSAID*, bile
Radiation	Radiation injury
Lymphocytic	Celiac disease, drug
Eosinophilic	Food allergies
Non-infectious granulomatous	Crohn's disease, sarcoidosis
Other infectious gastritis	Bacteria, viruses, fungi, parasite, TB, syphilis

\*Most common causes

### Clinical Features

- non-erosive gastritis is asymptomatic (except in certain rare causes like Crohn's Disease); difficult to diagnose clinically or endoscopically
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

### Management

- determined by etiology (see *H. Pylori* section, G13, *NSAID* section, G14 and *Stress-Induced Ulceration* section, G14)
- non-pharmacological: avoidance of mucosal irritants such as alcohol, NSAIDs and foods that trigger symptoms

## Peptic Ulcer Disease (PUD)



### Definition

- focal defects in the mucosal that penetrate the muscularis mucosa layer results in scarring (defects superficial to the muscularis mucosa have erosions and no scarring)
- peptic ulcer disease includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

### Etiology

**Table 6. Etiology of Peptic Ulcer Disease**

	Duodenal	Gastric
<i>H. pylori</i> infection	90%	60%
NSAIDs	7%	35%
Physiologic stress-induced	<3%	<5%
Zollinger-Ellison (ZE) syndrome	<1%	<1%
Idiopathic	15%	10%

- NSAID negative, *H. pylori* negative ulcers becoming more commonly recognized
- others: CMV, ischemic, idiopathic
- alcohol: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with tobacco, cirrhosis of liver, COPD and chronic renal failure

### Clinical Features

- dyspepsia: most common presenting symptom
  - only 20% of patients with dyspepsia have ulcers, while most have functional disease
- may present with complications
  - bleeding 10% (severe if from gastroduodenal artery) (see *Bleeding Peptic Ulcer*, G13)
  - perforation 2% (usually anterior ulcers)
  - gastric outlet obstruction 2%
  - penetration (posterior) 2%; may also cause pancreatitis
- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters over wk with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

### Investigations

- endoscopy (most accurate)
- upper GI series
- *H. pylori* tests (see Table 7)
- fasting serum gastrin measurement if Zollinger-Ellison (ZE) syndrome suspected

### Treatment

- specific management depends on etiology; (see *H. Pylori* section, G13, *NSAID* section, G14 and *Stress-Induced Ulceration* section, G14)
- eradicate *H. pylori* if present, chief advantage is to lower ulcer recurrence rate
- stop NSAIDs if possible
- start PPI: inhibits parietal cell  $H^+/K^+$ -ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other meds (e.g. histamine  $H_2$ -antagonists) less effective
- discontinue tobacco
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol and spices



#### Gastric vs. Duodenal Ulcers

Gastric ulcers must always be biopsied to rule out malignancies. Duodenal ulcers are rarely malignant.



#### Approach to PUD

- Stop NSAIDs
- Acid neutralization
- *H. pylori* eradication
- Quit smoking



#### Cigarette Smoking and PUD

- Increased risk of ulcer
- Increased risk of complications
- Increased chance of death from ulcer
- Impairs healing



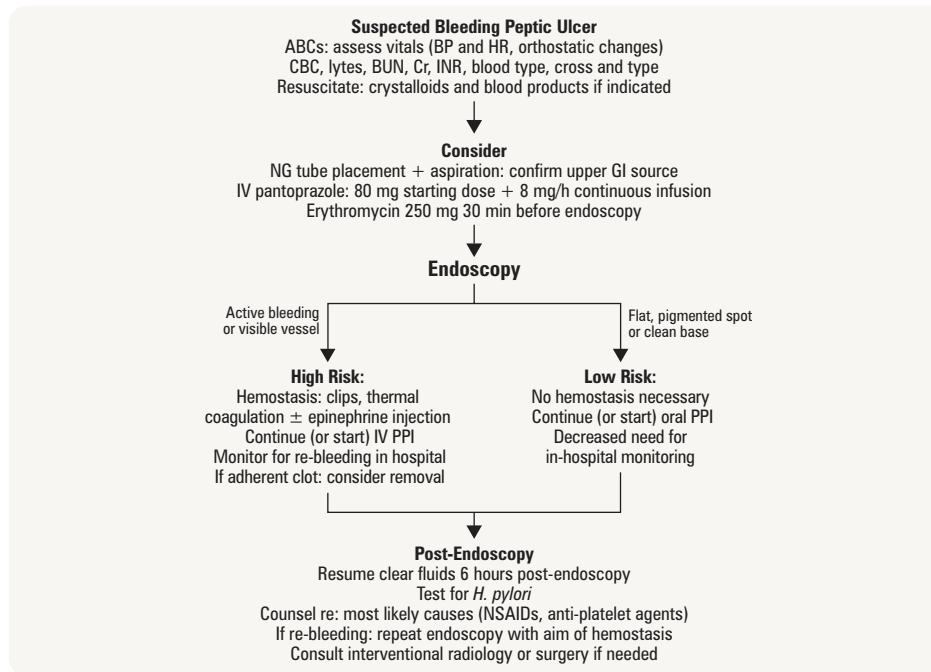
#### Bleeding Peptic Ulcers: Risk Factors for Increased Mortality

- Co-existent illness
- Hemodynamic instability
- Age > 60 yr
- Transfusion required



### Management of Bleeding Peptic Ulcers

- OGD to explore upper GI tract (see Figure 6)
- establish risk of rebleeding/continuous bleed
  - clinical risk factors: increased age (>60), bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
    - ♦ if high risk, consider ICU admission



**Figure 6. Approach to management of suspected bleeding peptic ulcer**

Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937



#### Intragastric pH with Oral vs. Intravenous Bolus plus Infusion Proton-pump Inhibitor Therapy in Patients with Bleeding Ulcers

Gastroenterology 2008;134:1836-1841

**Study:** Randomized control trial.

**Participants:** Patients presenting with overt bleeding from an ulcer.

**Intervention:** Patients received either IV lansoprazole (90 mg bolus followed by 9 mg/h infusion; n=32) or oral lansoprazole (120 mg bolus followed by 30 mg every 3 h; n=34).

**Primary Outcome:** 24 h pH.

**Results:** Intragastric pH was >6 for >60% of the study period in 22 (68.8%) patients receiving IV and 22 (64.7%) patients receiving oral PPI. At 1 h, mean pHs for IV and oral were 5.3 and 3.3, respectively (difference 2.0; P=0.001). After 1.5 h, there were no differences in mean pH between the groups. Mean pH rose above 6 after 2-3 h of IV PPI and 3-4 h of oral PPI.

**Conclusion:** Frequent oral PPI may be able to replace the currently recommended IV bolus plus infusion PPI therapy in patients with bleeding ulcers. However, IV PPI has a more rapid increase in pH, reaching mean pH of 6 approximately 1 h sooner than oral PPI.

## H. pylori-Induced Peptic Ulceration

### Pathophysiology

- *H. pylori*: Gram-negative flagellated rod that resides on but does not invade the gastric mucosa
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- mucosal defenses moderated by PGE2 and blood flow, mucus, etc.
- theories of how *H. pylori* causes ulcers: none satisfactory, but pattern of colonization correlates with outcome
  - gastritis only in antrum (15% of patients), high gastric acid, associated with peptic ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
  - gastritis throughout stomach ("pangastritis" – 85% of patients), low gastric acid, associated with cancer

### Epidemiology

- *H. pylori* is found in about 20% of all Canadians
  - highest prevalence in those raised during 1930s
- infection most commonly acquired in childhood, presumably by fecal-oral route
- high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

### Outcome

- gastritis (non-erosive) in 100% of patients but asymptomatic
- peptic ulcer in 15% of patients
- gastric malignancy [gastric carcinoma and mucosal associated lymphomatous tissue (MALT) lymphoma in 0.5% of patients]
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children <5 yr of age)

## Investigations

**Table 7. Diagnosis of *H. pylori* Infection**

Test	Sensitivity	Specificity	Comments
<b>Non-invasive Tests</b>			
Urea breath test	90-100%	89-100%	Affected by PPI therapy (false negatives)
Serology	88-99%	89-95%	Can remain positive after treatment
Stool antigen test	95-97%	94-98%	Useful for diagnosing acute infection
<b>Invasive Tests</b> (require endoscopy)			
Histology	93-99%	95-99%	Gold standard; affected by PPI therapy (false negatives)
Rapid urease test (on biopsy)	89-98%	93-100%	Rapid
Microbiology culture	98%	95-100%	Research only

### Treatment: *H. pylori* Eradication

- triple therapy for 7-14 d (Hp-Pac®): PPI bid (e.g. lansoprazole 30 mg bid) + amoxicillin 1 g bid + clarithromycin 500 mg bid
  - 80% success rate
- quadruple therapy for 10-14 d: PPI bid + bismuth 525 mg qid + tetracycline 500 mg qid + metronidazole 250 mg qid
  - only recommended as first line therapy if resistance to clarithromycin or metronidazole is high, or in patients with recent or repeated exposure to these drugs
  - levofloxacin can replace metronidazole or tetracycline
- sequential therapy
  - days 1-5: PPI bid + amoxicillin 1 g bid
  - days 6-10: PPI bid + clarithromycin 500 mg bid + tinidazole 500 mg bid
- 5-15% of cases are resistant to all known therapies

## NSAID-Induced Ulceration

- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
  - erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically silent: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

### Pathophysiology

- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (intravenous NSAID causes ulcers, but not erosions), inhibits mucosal cyclooxygenase, leading to decreased synthesis of protective prostaglandins, thus leading to ulcers

### Risk Factors For NSAID Causing Peptic Ulcer

- previous peptic ulcers/UGIB
- age
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

### Treatment

- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration



If at high risk for development of ulcers, prophylaxis with PPI indicated



**The David Y Graham Lecture: Use of Nonsteroidal Anti-inflammatory Drugs (NSAID) in a COX-2 Restricted Environment**

*Am J Gastroenterol* 2008;103:221-227

This short article reviews the current understanding of NSAID risks, emphasizing (1) with the possible exception of naproxen, all NSAIDs increase cardiovascular/cerebrovascular risk, especially the COX-2 specific inhibitors (2) low-dose Aspirin®, now used widely to decrease these risks, increases the likelihood of upper GI tract bleeding and may not abrogate the cardiovascular risk of NSAIDs (3) clopidogrel is no safer than Aspirin® in patients with high risk of upper GI tract bleeding (4) add a PPI to NSAID if there is an increased risk of upper GI events.

## Stress-Induced Ulceration

### Definition

- ulceration or erosion in the upper GI tract of ill patients, usually in ICU
- lesions most commonly in fundus of stomach

### Pathophysiology

- unclear: likely involves ischemia; may be caused by CNS disease, acid hypersecretion, Cushing ulcers
- physiological stress (e.g. fever, severe illness, complex post-op course) causes ulcers and erosions

**Risk Factors**

- mechanical ventilation
- anti-coagulation
- multi-organ failure
- septicemia
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface

**Clinical Features**

- UGIB (see *Upper Gastrointestinal Bleeding*, G25)
- painless

**Treatment**

- prophylaxis with gastric acid suppressants ( $H_2$ -blockers or PPI) decreases risk of UGIB, but may increase risk of pneumonia
- treatment same as for bleeding peptic ulcer but often less successful

**Gastric Carcinoma**

- see *General Surgery*, GS18

**Small and Large Bowel****Classification of Diarrhea****Definition**

- clinically: diarrhea defined as stools that are looser and/or more frequent than normal; physiologically: 24 h stool weight >200 g (less useful clinically)

**Classification**

- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) versus large volume (>1/2 cup stool; typical of small bowel diseases)
- watery (bowel disease) vs. steatorrhea
- secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)

**Acute Diarrhea****Definition**

- passage of frequent unformed stools for <14 d

**Etiology**

- most commonly due to infections
- most infections are self-limiting and resolve within 7 d

**Risk Factors**

- food (seafood, chicken, turkey, eggs, beef)
- medications: antibiotics, laxatives
- others: high risk sexual activity, infectious outbreaks, family history (IBD)

**Classification**

- broadly divided and classified into inflammatory and non-inflammatory diarrhea
- mechanisms:
  - stimulation of intestinal water secretion and inhibition of water absorption (i.e. secretory problem)
  - in inflammatory diarrhea, organisms and cytotoxins invade mucosa, killing mucosal cells, further perpetuating the diarrhea

**Table 8. Classification of Acute Diarrhea**

	Inflammatory	Non-Inflammatory
<b>Definition</b>	Disruption of intestinal mucosa	Intestinal mucosa intact
<b>Site</b>	Usually colon	Usually small intestine
<b>Sigmoidoscopy</b>	Usually abnormal mucosa seen	Usually normal
<b>Symptoms</b>	Bloody (not always) Small volume, high frequency Often lower abdominal cramping with urgency $\pm$ tenesmus May have fever $\pm$ shock	Watery, little or no blood Large volume Upper/periumbilical pain/cramp $\pm$ shock
<b>Investigations</b>	Fecal WBC and RBC positive	Fecal WBC negative

**Useful Questions in Acute Diarrhea****Those Fads Wilt**

Travel  
Homosexual contacts  
Outbreaks  
Seafood  
Extra-intestinal signs of IBD  
Family history  
Antibiotics  
Diet  
Steatorrhea  
Weight loss  
Immunosuppressed  
Laxatives  
Tumour history

**Infectious Causes of Inflammatory Diarrhea****"Your Stool Smells Extremely Crappy"**

*Yersinia*  
*Shigella*  
*Salmonella*  
*E. coli* (EHEC 0157:H7), *E. histolytica*  
*Campylobacter*, *C. difficile*

**Table 8. Classification of Acute Diarrhea** (continued)

	Inflammatory	Non-Inflammatory
<b>Etiology</b>	See <i>Differential Diagnosis of Common Presenting Complaints, G4</i>	See <i>Differential Diagnosis of Common Presenting Complaints, G4</i>
<b>Differential Diagnosis</b>	Acute presentation of idiopathic inflammatory bowel disease	Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease)
<b>Significance</b>	Higher yield with stool C&S Can progress to life-threatening megacolon, perforation, hemorrhage Antibiotics may benefit	Lower yield with stool C&S Chief life-threatening problem is electrolyte disturbances/ fluid depletion Antibiotics unlikely to be helpful

**Investigations**

- stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (day care worker, nursing home resident, etc.)
  - C&S only tests *Campylobacter*, *Salmonella*, *Shigella*, *E. Coli*
    - ♦ other organisms must be ordered separately
- flexible sigmoidoscopy: useful if inflammatory diarrhea suspected
  - biopsies are the most useful method of distinguishing idiopathic IBD (Crohn's disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- *C. difficile* toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home or recent chemotherapy

**Treatment**

- fluid and electrolyte replacement orally in most cases, intravenous if severe extremes of age/coma
- anti-diarrheals
  - antimitility agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
    - ♦ side effects: abdominal cramps, toxic megacolon
  - absorbants: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
    - ♦ act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
    - ♦ much less effective than antimitility agents
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful
- antibiotics: rarely indicated
  - risks
    - ♦ prolonged excretion of enteric pathogen (especially *Salmonella*)
    - ♦ drug side effects (including *C. difficile* infection)
    - ♦ development of resistant strains
    - ♦ renal failure/hemolysis (enterohemorrhagic *E. Coli* O157:H7)
  - indications for antimicrobial agents in acute diarrhea:
    - ♦ septicemia
    - ♦ prolonged fever with fecal blood or leukocytes
    - ♦ clearly indicated: *Shigella*, *V. cholerae*, *C. difficile*, traveller's diarrhea [enterotoxigenic *E. coli* (ETEC)], *Giardia*, *Entamoeba histolytica*, *Cyclospora*
    - ♦ situational: *Salmonella*, *Campylobacter*, *Yersinia*, non-enterotoxigenic *E. coli*
    - ♦ *Salmonella*: always treat *Salmonella typhi* (typhoid or enteric fever); treat other *Salmonella* only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease

**Stool Osmotic Gap**

Stool osmolality is normally about 290 mOsm/kg and can be approximated by the calculated stool osmolality ( $2 \times [\text{Na}^+]_{\text{stool}} + [\text{K}^+]_{\text{stool}}$ ). In osmotic diarrhea, measured stool osmolality > calculated stool osmolality. In secretory diarrhea measured stool osmolality = calculated stool osmolality.



*S. typhi* has a rose spot rash (transient maculopapular rash on anterior thorax, upper abdomen), and a prodrome of high fever, bradycardia, headache and abdominal pain. Diarrhea is not the initial presentation.

## Traveller's Diarrhea

- see [Infectious Diseases, ID14](#)

## Chronic Diarrhea

**Definition**

- passage of frequent unformed stool for >14 d
- approach is similar to that of acute diarrhea except that the majority of cases are non-infectious

**Etiology/Classification**

- see *Differential Diagnosis of Common Presenting Complaints, G4*

**Investigations**

- guided by history
- stool analysis for: *C. difficile* toxin, C&S, O&P ± fecal fat, WBC
- blood for: CBC, electrolytes, CRP, TSH, celiac serology (anti-tTG, protein electrophoresis, IgA)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (last resort – very costly)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease



## Maldigestion and Malabsorption



### Definition

- **maldigestion:** inability to break down large molecules in the lumen of the intestine into their component small molecules
- **malabsorption:** inability to transport molecules across the intestinal mucosa into circulation
- **malassimilation:** encompasses both maldigestion and malabsorption

### Etiology

- **maldigestion**
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis, cancer)
  - bile salt deficiency
    - ♦ terminal ileal disease (impaired recycling), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic)
  - specific enzyme deficiencies (e.g. lactase)
- **malabsorption**
  - inadequate absorptive surface
    - ♦ infections/infestations (e.g. Whipple's disease, Giardia)
    - ♦ immunologic or allergic injury (e.g. celiac disease)
    - ♦ infiltration (e.g. lymphoma, amyloidosis)
    - ♦ fibrosis (e.g. systemic sclerosis, radiation enteritis)
    - ♦ bowel resection
    - ♦ extensive Crohn's disease
  - drug-induced
    - ♦ cholestyramine, ethanol, neomycin, tetracycline and other antibiotics
  - endocrine
    - ♦ diabetes (complex pathogenesis)

### Clinical Features

- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency (see Table 9)



Fat Soluble Vitamins: **ADEK**  
vitamin A, vitamin D, vitamin E, vitamin K

**Table 9. Absorption of Nutrients and Fat Soluble Vitamins**

Deficiency	Absorption	Signs and Symptoms	Investigations
<b>Iron</b>	Duodenum, upper jejunum	Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica	↓ Hb, ↓ serum Fe, ↓ serum ferritin
<b>Calcium</b>	Duodenum, upper jejunum (binds to $\text{Ca}^{2+}$ binding-protein in cells; levels increased by Vit D)	Metabolic bone disease, may get tetany and paresthesias if serum calcium falls (see <a href="#">Endocrinology</a> , E40)	↓ serum $\text{Ca}^{2+}$ , ↓ serum $\text{Mg}^{2+}$ , and ↑ ALP Evaluate for ↓ bone mineralization radiographically (DEXA)
<b>Folic acid</b>	Jejunum	Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)	↓ serum folic acid
<b>Vitamin B<sub>12</sub></b>	B <sub>12</sub> ingested and bound to R proteins mainly from salivary glands; stomach secretes intrinsic factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B <sub>12</sub> -IF complex forms, protecting B <sub>12</sub> from further protease attack; B <sub>12</sub> absorbed in ileum and binds to transcobalamin (TC)	Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis	Differentiate causes by Schilling test when available Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see <a href="#">Hematology</a> , H22)
<b>Carbohydrate</b>	Complex polysaccharides hydrolyzed to oligosaccharides and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum	Generalized malnutrition, weight loss, flatus and diarrhea	Hydrogen breath test Trial of carbohydrate-restricted diet D-xylose test
<b>Protein</b>	Digestion at stomach, brush border, and inside cell Absorption occurs primarily in the jejunum	General malnutrition and weight loss, amenorrhea and ↓ libido if severe	↓ serum albumin (low sensitivity)
<b>Fat</b>	Lipase, colipase, phospholipase A (pancreatic enzymes) and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Fatty acids diffuse into cell cytoplasm	Generalized malnutrition, weight loss and diarrhea Foul-smelling feces + gas Steatorrhea	Small bowel biopsy MRCP, ERCP, pancreatic function tests Quantitative stool fat test (72 h) (Sudan stain of stool) (C-triolein breath test)
<b>Vitamin A</b>	Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)	Night blindness Dry skin Keratomalacia	
<b>Vitamin D</b>	Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)	Osteomalacia in adults Rickets in children	
<b>Vitamin E</b>	Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)	Retinopathy, neurological problems	
<b>Vitamin K</b>	Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation	Prolonged INR causes bleeding	

\* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone

## Investigations

- transglutaminase serology/protein electrophoresis and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea
- serum carotene, folate,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , vitamin  $\text{B}_{12}$ , albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear stained with Sudan (rarely used)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)
- trial of therapy with pancreatic enzymes

## Treatment

- dependent on underlying etiology

# Celiac Disease (Gluten Enteropathy/Sprue)

## Definition

- abnormal small intestine mucosa due to intestinal reaction to gliadin, a component of gluten found in cereal grains

## Etiology

- only autoimmune disease in which antigen ( $\alpha$ -gliadin) is recognized
- associated with other autoimmune diseases, especially thyroid disease
- gluten, a protein in cereal grains, broken down to gliadin, is toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; also associated with HLA-DQ8

## Epidemiology

- more common in women
- family history: 15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy

## Clinical Features

- classically: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; now more commonly bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
  - thus iron, calcium and folic acid deficiency more common than vitamin  $\text{B}_{12}$  deficiency
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

## Investigations

- small bowel mucosal biopsy (usually duodenum) is diagnostic with:
  - villous atrophy and crypt hyperplasia
  - increased number of plasma cells and lymphocytes in lamina propria
  - increased intraepithelial lymphocytes
  - villous atrophy also seen in small bowel overgrowth, Crohn's, lymphoma, Giardia, HIV
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation,  $\text{Ca}^{2+}$ , Fe, albumin, cholesterol, carotene,  $\text{B}_{12}$  absorption
- improvement with a gluten-free diet; should not be started before anti-tTG and biopsy
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - IgA deficient patients have false-negative anti-tTG
    - thus measure serum IgA concomitantly (via serum protein electrophoresis)
- fecal fat >7%

## Treatment

- dietary counselling
  - gluten free diet: avoid barley, rye, wheat
    - oats allowed if not contaminated by other grains
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
- if poor response to diet change, consider:
  - alternate diagnosis
  - non-adherence to gluten-free diet
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)



### Gluten found in "BROW"

Barley  
Rye  
Oats (controversial)  
Wheat



### Gluten Microchallenge with Wheat-based Starch Hydrolysates in Celiac Disease Patients

*Aliment Pharm Therap* 2008;28:1240-1248

**Study:** Randomized, placebo-controlled, prospective study with 24 wk follow-up.

**Participants:** 90 patients with celiac disease in remission.

**Intervention:** Patients either received glucose syrups, maltodextrins or placebo.

**Primary Outcome:** Small bowel mucosal morphology and inflammation, symptoms, celiac serology and malabsorption.

**Results:** There were no significant differences between the intervention and control group in small-bowel morphology and inflammation, gastrointestinal symptoms, serology or malabsorption parameters.

**Conclusion:** Celiac patients can safely continue to consume wheat-based starch hydrolysates, glucose syrups and maltodextrins.



- development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
- development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)

### Prognosis

- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon)
- risk of malignancy may be lowered by dietary gluten restriction

## Inflammatory Bowel Disease (IBD)



### Definition

- Crohn's disease, ulcerative colitis, indeterminate colitis

### Pathophysiology

- poorly understood
- sustained response of the immune system, perhaps to enteric flora in a genetically predisposed individual
- current hypothesis: lack of appropriate down-regulation of immune responsiveness

### Genetics

- increased risk of both UC and CD in relatives of patients with either disease, especially siblings, early onset disease
  - familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 9 gene loci described to be associated
- CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially Ashkenazi Jews, early onset disease, ileal involvement, fistulizing and stenotic disease
  - CARD15 gene product modulates NFκB, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

### Clinical Features

**Table 10. Clinical Differentiation of Ulcerative Colitis from Crohn's Disease**

	Crohn's Disease	Ulcerative Colitis
<b>Location</b>	Any part of GI tract <ul style="list-style-type: none"> <li>• Small bowel + colon: 50%</li> <li>• Small bowel only: 30%</li> <li>• Colon only: 20%</li> </ul>	Isolated to large bowel Always involves rectum, may progress proximally
<b>Rectal Bleeding</b>	Uncommon	Very common (90%)
<b>Diarrhea</b>	Less prevalent	Frequent small stools
<b>Abdominal Pain</b>	Post-prandial/colicky	Less common
<b>Fever</b>	Common	Uncommon
<b>Urgency/Tenesmus</b>	Uncommon (unless rectum involved)	Common
<b>Palpable Mass</b>	Frequent (25%), RLQ	Rare (if present, cecum full of stool)
<b>Recurrence After Surgery</b>	Common	None post-colectomy
<b>Endoscopic Features</b>	Ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning	Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps
<b>Histologic Features</b>	Transmural distribution with skip lesions Focal inflammation ± noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures Glands intact	Mucosal distribution, continuous disease (no skip lesions) Granulomas absent Gland destruction, crypt abscess
<b>Radiologic Features</b>	Cobblestone mucosa Frequent strictures and fistulae AXR: Bowel wall thickening "string sign"	Lack of haustra Strictures rare and suggests complicating cancer
<b>Complications</b>	Strictures, fistulae, perianal disease	Toxic megacolon
<b>Colon Cancer Risk</b>	Increased if >30% of colon involved	Increased except in proctitis

**Table 11. Extraintestinal Manifestations (EIM) of IBD**

System	Crohn's Disease	Ulcerative Colitis
<b>Dermatologic</b>		
Erythema Nodosum	15%	10%
Pyoderma Gangrenosum	10%	Less common
Perianal skin tags	75-80%	Rare
Oral mucosal lesions	Common	Rare
Psoriasis	Statistically associated in 5-10% of those with IBD but not an EIM	
<b>Rheumatologic</b>		
Peripheral arthritis	15-20% of those with IBD (CD>UC)	
Ankylosing Spondylitis	10% of those with IBD (CD>UC)	
Sacroiliitis	Occurs equally in CD and UC	
<b>Ocular</b> (~10% of IBD)		
Uveitis (vision threatening)		
Episcleritis (benign)	3-4% of IBD patients (CD>UC)	
<b>Hepatobiliary</b>		
Cholelithiasis	15-35% of patients with ileal Crohn's	
Primary sclerosing cholangitis (PSC)	1-5% of IBD cases involving colon	
Fatty liver		
<b>Urologic</b>		
Calculi	Most common in CD, especially following ileal resection	
Ureteric obstruction		
Fistulae	Characteristic of Crohn's	
<b>Others</b>		
Thromboembolism		
Vasculitis		
Osteoporosis		
Vitamin deficiencies (B <sub>12</sub> , Vit ADEK)		
Cardiopulmonary disorders		
Pancreatitis (rare)		

## Crohn's Disease (CD)

### Definition

- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region ("gum to bum")

### Epidemiology

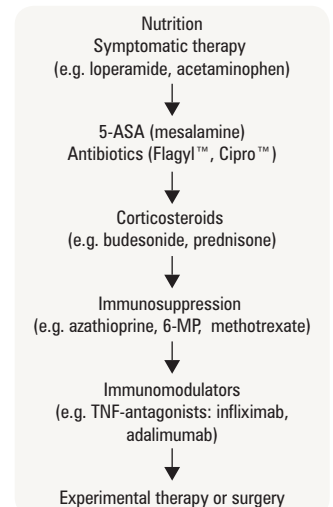
- incidence 1-6/100,000; prevalence 10-100/100,000
- bimodal: onset before 30 yr, second smaller peak age 60; M=F
- incidence of Crohn's increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in Crohn's patients is higher than general population

### Clinical Features

- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- most often presents as recurrent episodes of abdominal cramps, diarrhea and weight loss
- most common location: ileum + ascending colon
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- fistulae, fissures, abscesses are common
- extra-intestinal manifestations (see Table 11) are more common with colonic involvement
- linear ulcers leading to mucosal islands and "cobblestone" appearance
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina and other parts of bowel
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

### Investigations

- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response
- bacterial cultures, O&P, *C. difficile* toxin to exclude other causes of inflammatory diarrhea



**Figure 7. Traditional graded approach to induction therapy in Crohn's disease**

Note: Starting with immunosuppressives plus immunomodulators ("bottom-up approach") increasingly being used (Lancet 2008;371:660-667). Combination of azathioprine and infliximab has the highest remission rate yet described with medical treatment (NEJM 2010;362:1383-1395).



Characteristically more than 1 yr between onset of symptoms and diagnosis of Crohn's disease.

**Management** (also see Figure 7)**Table 12. Management of Crohn's Disease**

Management	Notes
<b>Lifestyle/Diet</b>	Smoking cessation Fluids only during acute exacerbation Enteral diets may aid in remission No evidence for any non-enteral diet changing the natural history of Crohn's disease, but may affect symptoms Those with extensive small bowel involvement or extensive resection require electrolyte, mineral and vitamin supplements (vit D, $\text{Ca}^{2+}$ , $\text{Mg}^{2+}$ , zinc, Fe, $\text{B}_{12}$ )
<b>Antidiarrheal Agents*</b>	Loperamide (Imodium®) > diphenoxylate (Lomotil®) > codeine (cheap but addictive) All work by decreasing small bowel motility Caution if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups
<b>5-ASA</b>	Efficacy controversial: most evidence for mild colonic disease Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine Hydrolysis by intestinal bacteria releases 5-ASA (active component) Dose-dependent efficacy Mesalamine (Pentasa®): coated 5-ASA releases 5-ASA in the ileum and colon
<b>Antibiotics</b>	e.g. metronidazole (20 mg/kg/d, bid or tid dosing) or ciprofloxacin Best described for perianal Crohn's, although characteristically relapse when discontinued
<b>Corticosteroids</b>	Prednisone: starting dose 40 mg OD for acute exacerbations; IV methylprednisolone if severe No proven role for steroids in maintaining remissions; masks intra-abdominal sepsis
<b>Immunosuppressives</b>	6-mercaptopurine (6-MP), azathioprine (Imuran®); methotrexate (used less often) More often used to maintain remission than to treat active inflammation Most commonly used as steroid-sparing agents i.e. to lower risk of relapse as corticosteroids are withdrawn May require >3 mo to have beneficial effect; usually continued for several years May help to heal fistulae, decrease disease activity Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy
<b>Biologics</b>	Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF- $\alpha$ Proven effective for treatment of fistulae and patients with medically refractory CD First-line immunosuppressive therapy with infliximab + azathioprine more effective than using either alone
<b>Surgical/Experimental</b>	Surgical treatment (see <a href="#">General Surgery</a> , GS30) Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding and for medically refractory disease If <50% or <200 cm of functional small intestine, risk of short bowel syndrome At least 50% clinical recurrence within 5 yr; 85% within 15 yr; endoscopic recurrence rate even higher 40% likelihood of second bowel resection, 30% likelihood of third bowel resection Complications of ileal resection: <100 cm resected → watery diarrhea (impaired bile salt absorption) Treatment: cholestyramine or anti-diarrheals e.g. loperamide >100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency) Treatment: fat restriction, medium chain triglycerides

\*Cholestyramine: a bile-salt binding resin; for watery diarrhea with <100 cm of terminal ileum diseased or resected; however, non-specific anti-diarrheals are more convenient and often more potent

**Traditional Medical Management of Crohn's**

	Induction of Remission	Maintenance
5-ASA	?	?
Steroids	+	
Immunosuppressive	+	+
Antibiotics	+	
MTX	+	+
Infliximab	+	+

**Biological Therapies for Inflammatory Bowel Diseases**

*Gastroenterology* 2009;136:1182-1197

Although the etiology of inflammatory bowel diseases (IBD) is unknown, biological therapies (BT) that target key molecules in innate and adaptive immune pathways have been designed.

**Anti-TNF Agents** (infliximab, adalimumab, certolizumab): Effective in CD, less effective for UC. Increase mucosal healing, decrease need for hospitalizations and surgeries, and can induce steroid-free remission. At least 10% of patients annually develop intolerance and/or a loss of response.

**Selective Anti-Adhesion Molecules** (natalizumab): Increases response and remission rates, circulating leukocytes and steroid-sparing capacity in CD. Progressive multifocal leukoencephalopathy is a rare adverse event.

**Promising New BT:** Anti-Interleukin-12/Interleukin-23 p40 target factors more often associated with CD, while anti-IFN-antibodies may treat CD and UC.

**BT Without Established Efficacy:** Recombinant human cytokines, blockade of T-cell activation (daclizumab and basiliximab) and stimulators of the innate immune system.

**Conclusion:** Anti-TNF agents are effective treatments for IBD. There is a need to develop salvage biologic therapies for patients who do not respond to a first biological drug. BT's have a safety risk, so their place in treatment algorithms must be defined carefully.

**Prognosis**

- highly variable course
- 10% disabled by the disease eventually; spontaneous remission also described
- increased mortality, especially with more proximal disease; greatest in the first 4-5 yr
- complications include:
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as ulcerative colitis (see below) if more than 1/3 of colon involved

## Ulcerative Colitis (UC)



### Definition

- inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

### Epidemiology

- incidence 2-10/100,000; prevalence 35-100/100,000 (more common than Crohn's)
- 2/3 onset by age 30 (with second peak after 50); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- risk is less in smokers
- inflammation limited to rectum or left colon is more common than pancolitis

### Pathology

- disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
- inflammation seen is diffuse, continuous and confined to mucosa

### Clinical Features

- rectal bleeding is the hallmark feature, however diarrhea may be present if more than the rectum is involved
  - can also have abdominal cramps/pain, especially with defecation
- severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
- tenesmus, urgency, incontinence
- systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
- extra-intestinal manifestations (see Table 11)
- characteristic exacerbations and remissions; 5% of cases are fulminant



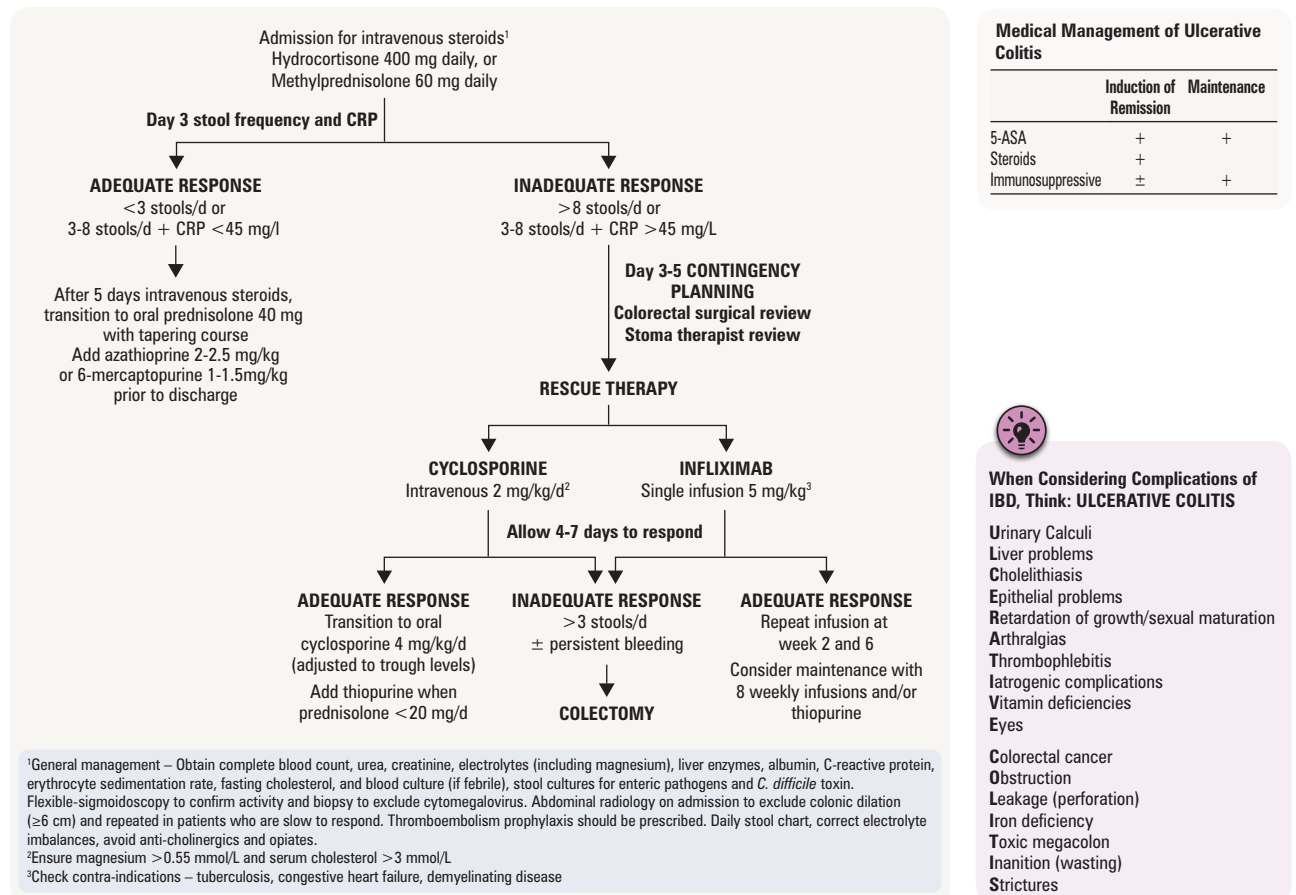
In UC, non-bloody diarrhea is frequently the initial presentation; eventually progressing to bloody diarrhea.

### Investigations

- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, *C. difficile* toxin assay necessary to exclude infection
- no single confirmatory test

### Management

- mainstays of treatment: 5-ASA (mesalamine) derivatives and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- diet of little value in decreasing inflammation but may alleviate symptoms
- antidiarrheal medications generally not indicated in UC
- 5-ASA
  - topical (suppository or enema): very effective for distal disease (distal to splenic flexure), preferable to corticosteroids
  - oral: effective for mild to moderate, but not severe colitis (4 g/d)
  - e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d
  - commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
  - may decrease rate of colorectal cancer
- corticosteroids
  - to remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h)
  - limited role as maintenance therapy
  - use suppositories for proctitis, enemas for proctosigmoiditis
  - topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants (steroid-sparing)
  - if severe UC is refractory to steroid therapy, consider adding IV cyclosporine or IV infliximab within 3-5 d of recognition of need for salvage – rapidly effective, but helpful only in a minority of patients
  - azathioprine: too slow to rapidly resolve acute relapse
    - most commonly used to induce and maintain remission as corticosteroids withdrawn
- surgical treatment
  - early in severe UC, especially fulminant cases and toxic megacolon – consider operation if no response after 3-5 d of corticosteroids, or after 4-7 d of immunosuppressive medical therapy
  - aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastomosis
  - indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids



<sup>1</sup>General management – Obtain complete blood count, urea, creatinine, electrolytes (including magnesium), liver enzymes, albumin, C-reactive protein, erythrocyte sedimentation rate, fasting cholesterol, and blood culture (if febrile), stool cultures for enteric pathogens and *C. difficile* toxin. Flexible-sigmoidoscopy to confirm activity and biopsy to exclude cytomegalovirus. Abdominal radiology on admission to exclude colonic dilation (≥6 cm) and repeated in patients who are slow to respond. Thromboembolism prophylaxis should be prescribed. Daily stool chart, correct electrolyte imbalances, avoid anti-cholinergics and opiates.

<sup>2</sup>Ensure magnesium >0.55 mmol/L and serum cholesterol >3 mmol/L

<sup>3</sup>Check contra-indications – tuberculosis, congestive heart failure, demyelinating disease

**Medical Management of Ulcerative Colitis**

	Induction of Remission	Maintenance
5-ASA	+	+
Steroids	+	
Immunosuppressive	±	+

**When Considering Complications of IBD, Think: ULCERATIVE COLITIS**

Urinary Calculi  
Liver problems  
Cholelithiasis  
Epithelial problems  
Retardation of growth/sexual maturation  
Arthralgias  
Thrombophlebitis  
Iatrogenic complications  
Vitamin deficiencies  
Eyes

Colorectal cancer  
Obstruction  
Leakage (perforation)  
Iron deficiency  
Toxic megacolon  
Inanition (wasting)  
Strictures

**Figure 8. Medical management of severe ulcerative colitis**

Gastroenterology 2011;140:1827-1837

## Complications

- similar to CD, except:
  - more liver problems (especially primary sclerosing cholangitis in men)
  - greater risk of colorectal cancer
    - ♦ risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%)
    - ♦ risk also increases with active mucosal inflammation and sclerosing cholangitis
    - ♦ thus, regular colonoscopy and biopsy in pancolitis of ≥8 yr is indicated
  - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see [General Surgery](#), GS26)

## Prognosis

- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st year correlates with increased severity of attacks and increased colectomy rate
  - colectomy rate = 1% for all patients after the 1st year; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course



## Irritable Bowel Syndrome (IBS)

### Definition

- a form of functional bowel disease, more than just a label for GI symptoms unexplained after investigations

### Epidemiology

- 20% of North Americans
- onset of symptoms usually in young adulthood
- F>M

### Pathophysiology

- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associations or if causative
- psychological: stress may increase IBS symptoms but does not cause IBS

### Diagnosis

**Table 13. Rome III Criteria for Diagnosing Irritable Bowel Syndrome**

#### IBS Rome III Criteria

- $\geq 12$  wk in the past 12 mo of abdominal discomfort or pain that has 2 out of 3 features:
  - Relieved with defecation
  - Associated with a change in frequency of stool
  - Associated with a change in consistency of stool
- The following are supportive, but not essential to the diagnosis:
  - Abnormal stool frequency ( $>3/d$  or  $<3/wk$ )
  - Abnormal stool form (lumpy/hard/loose/watery)  $>1/4$  of defecations
  - Abnormal stool passage (straining, urgency, feeling of incomplete evacuation)  $>1/4$  of defecations
  - Passage of mucus  $>1/4$  of defecations
  - Bloating

#### Diagnosis of IBS Less Likely in Presence of "Red Flag" Features

- Weight loss
- Fever
- Nocturnal defecation
- Anemia
- Blood or pus in stool
- Abnormal gross findings on flexible sigmoidoscopy

#### Normal Physical Exam

### Investigations

- if history consistent with Rome III criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS
- CBC, TSH, albumin, CRP, tTG serology with protein electrophoresis
- stool for C&S, O&P, fat excretion if diarrhea present
- consider sigmoidoscopy

### Management

- reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction
- no therapeutic agent consistently effective, pain most difficult to control
- symptom-guided treatment
  - pain predominant
    - ♦ antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine)
    - ♦ increase dietary fibre (bran or psyllium)
    - ♦ tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI)
  - diarrhea predominant
    - ♦ increase dietary fibre (bran or psyllium) to increase stool consistency
    - ♦ loperamide (Imodium®)
    - ♦ diphenoxylate (Lomotil®)
    - ♦ cholestyramine 4 g QID
  - constipation predominant
    - ♦ exercise and increase fibre in diet
    - ♦ osmotic or other laxatives

### Prognosis

- 80% improve over time
- most have intermittent episodes
- normal life expectancy



#### IBS Mimickers

- Enteric infections e.g. *Giardia*
- Lactose intolerance/other disaccharidase deficiency
- Crohn's disease
- Celiac sprue
- Drug-induced diarrhea
- Diet-induced (excess tea, coffee, colas)

## Constipation



### Definition

- passage of infrequent or hard stools with straining (stool water  $<50$  mL/d); bowel frequency  $<3$  times/wk

### Epidemiology

- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries



## Etiology

- most common: idiopathic attributed to colon dysmotility but this is difficult to measure
- organic causes
  - medication side effects (narcotics, antidepressants) are the most common
  - intestinal obstruction, left sided colon cancer (consider in older patients) and fecal impaction
  - metabolic
    - ♦ diabetes mellitus
    - ♦ hypothyroidism
    - ♦ hypercalcemia, hypokalemia, uremia
  - neurological
    - ♦ intestinal pseudo-obstruction
    - ♦ Parkinson's disease
    - ♦ multiple sclerosis
  - collagen vascular disease (e.g. scleroderma)
  - painful anal conditions (e.g. fissures)

## Clinical Presentation

- overlaps with irritable bowel syndrome
- abdominal pain relieved by defecation, hard stools, straining and pain with defecation, flatulence, overflow diarrhea, tenesmus (sense of incomplete evacuation), abdominal distention, <3 BM/wk

## Investigations

- consider colon visualization (colonoscopy, CT colonography), although chronic constipation by itself is rarely due to colonic mucosal disease
- classification based on colon transit time, can be quantitated by swallowing radio-opaque markers to measure colonic transit time (normal: 70 h)
  - (1) normal = misperception of normal defecation (irritable bowel syndrome)
  - (2) prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
  - (3) outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- combination of (2) and (3) common

## Treatment (in order of increasing potency)

- dietary fibre
  - useful if mild or moderate constipation, but not if severe
  - aim for 30 g daily, increase dose slowly
- surface-acting (soften and lubricate)
  - docusate salts, mineral oils
- osmotic agents (effective in 2-3 d)
  - lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, aka milk of magnesia), lactitol, polyethylene glycol 3350
- cathartics/stimulants (effective in 24 h)
  - castor oil, senna (avoid prolonged use to prevent melanosis coli), bisacodyl
- enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl suppository)



### Causes of Constipation

#### DOPED

Drugs

Obstruction

Pain

Endocrine dysfunction

Depression

## Upper Gastrointestinal Bleeding



### Definition

- bleeding proximal to the ligament of Treitz (75% of GI bleeds)
  - ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

### Etiology

- above the GE junction
  - epistaxis
  - esophageal varices (10-30%)
  - esophagitis
  - esophageal cancer
  - Mallory-Weiss tear (10%)
- stomach
  - gastric ulcer (20%) (see *Peptic Ulcer Disease*, G12)
  - gastritis (e.g. from alcohol or post-surgery) (20%)
  - gastric cancer
  - gastric antral vascular ectasia (rare, associated with cirrhosis and CTD)
  - dieulafoy lesion (very rare)



**Aortoenteric Fistula** is a rare and lethal cause of GI bleed, most common in patients with a history of aortic graft surgery. Therefore, perform emergency endoscopy if suspected, emergency surgery if diagnosed.

**Note:** The window of opportunity is narrow. Suspect if history of aortic graft, abdominal pain associated with bleeding.

- duodenum
  - ulcer in bulb (25%)
  - aortoenteric fistula: usually only if previous aortic graft (see sidebar)
- coagulopathy (drugs, renal disease, liver disease)
- vascular malformation (Dieulafoy's lesion, AVM)

### Clinical Features

- in order of decreasing severity of the bleed: hematochezia > hematemesis > coffee ground emesis > melena > occult blood in stool

### Management (initial)

- stabilize patient (1-2 large bore IVs, IV fluids, monitor)
- send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
- keep NPO
- consider NG tube to determine upper vs. lower GI bleeding in some cases
- endoscopy (OGD): establish bleeding site + treat lesion
  - if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  - endoclips
- IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  - given to stabilize clot, not to accelerate ulcer healing
  - if given before endoscopy, decreases need for endoscopic therapeutic intervention
- for variceal bleeds, octreotide 50 µg loading dose followed by constant infusion of 50 µg/h
- consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach

### Prognosis

- 80% stop spontaneously
- peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
- endoscopic predictors of rebleeding: spurt or ooze, visible vessel, fibrin clot
- can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no predictors of rebleeding
- H<sub>2</sub>-antagonists have little impact on rebleeding rates and need for surgery
- esophageal varices have a high rebleeding rate (55%) and mortality (29%)



Always ask about NSAID/Aspirin® or anticoagulant therapy in GI bleed.



### Forrest Classification of Bleeding Peptic Ulcers

Forrest Class	Type of lesion	Risk of Rebleed (%)
I	Arterial bleeding (oozing/spurting)	55-100
Ila	Visible vessel	43
Ilb	Sentinel clot	22
Ilc	Hematin covered flat spot	10
III	No stigmata of hemorrhage	5

Lancet 1974;2:394-397



### Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

NEJM 2013;368:11-21

**Study:** Prospective, unblinded, RCT, follow-up up to 45 d.

**Populations:** 921 patients with hematemesis, bloody nasogastric aspirate, melena or both. Exclusion criteria included massive bleed, ACS, stroke/TIA or transfusion within previous 90 d; recent trauma/surgery; lower GI bleed.

**Intervention:** Patients randomized to restrictive (<70 g/L) or liberal (<90 g/L) transfusion.

**Outcome:** Mortality, further bleeding, adverse events.

**Results:** Fewer patients in the restrictive group required transfusion (51% vs. 15%;  $P < 0.001$ ). The hazard ratio for death for restrictive compared to liberal transfusion was 0.55; 95% CI, 0.33 to 0.92;  $P = 0.02$ . Further bleeding occurred in 10% vs. 16% ( $P = 0.01$ ) of patients, while adverse effects occurred in 40% vs. 48% ( $P = 0.02$ ) of patients in the restrictive and liberal strategies, respectively. The restrictive strategy had a better survival rate in patients with bleeding associated with cirrhosis Child-Pugh class A or B (HR: 0.30; 95% CI, 0.11 to 0.85), but not in cirrhosis Child-Pugh class C (HR: 1.04; 95% CI, 0.45 to 2.37) or a peptic ulcer (HR: 0.70; 95% CI, 0.26 to 1.25).

**Conclusions:** Transfusing patients with an acute upper GI bleed at hemoglobin of <70 g/L rather than 90 g/L is associated with fewer transfusions, better survival, and fewer adverse events.



### Review Article: Improved Survival with Patients with Variceal Bleeds

Int J Hepatol 2011;doi=10.461/2011/356919

**General measures:** Resuscitation to achieve hemodynamic stability (Hb >70-80 g/L) but avoid fluid overload as it can precipitate or worsen ascites.

**Antibiotic prophylaxis:** IV ceftriaxone or postendoscopic norfloxacin reduces bacterial infection, rebleeding rates, length of hospitalization, and all-cause mortality.

**Splanchnic vasoconstriction:** Somatostatin, Octreotide, Terlipressin.

**Therapeutic Endoscopy:** Band ligation is superior to injection sclerotherapy in initial control of bleeding, incidence of rebleeding, side effects, time, and survival.

Combination therapy with vasoactive drug plus endoscopic band ligation is recommended for Child's A and if combined therapy fails (HVPG >20 mmHg within 24 h after start of bleed is the best predictor failure); TIPS is then recommended for patients with Child's B or C, early TIPS is recommended over combined therapy.

## Approach to Iron Deficiency Anemia

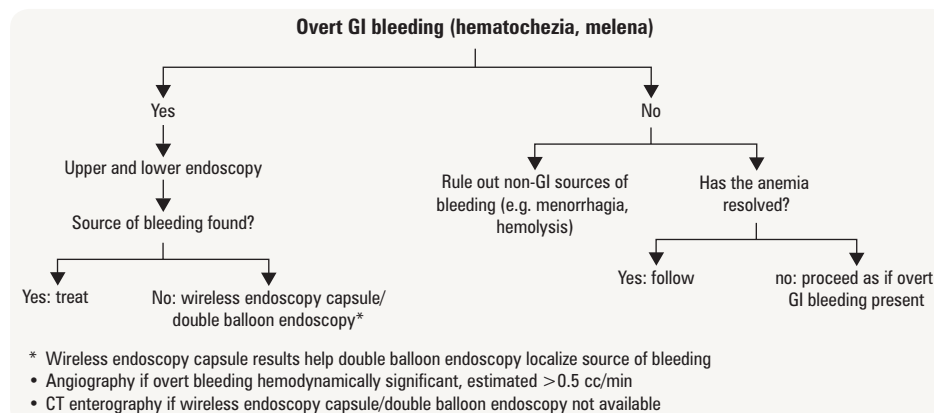


Figure 9. Approach to iron deficiency anemia

## Esophageal Varices

### Etiology

- almost always due to portal hypertension
- often accompanied by varices in stomach

### Clinical Features

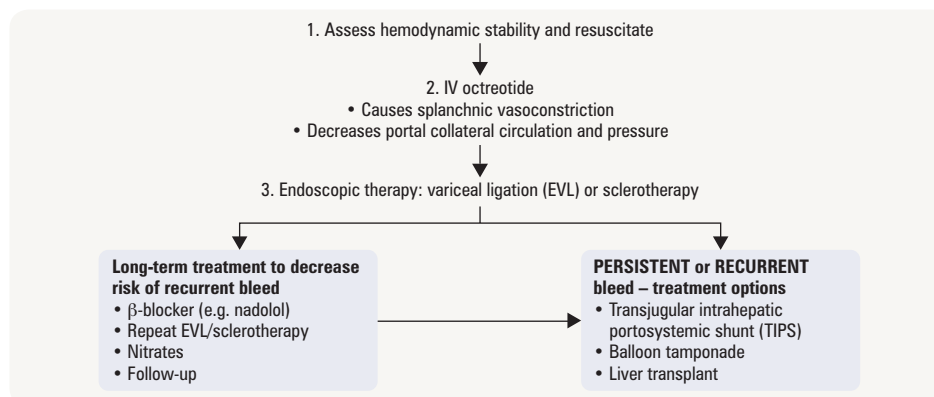
- characteristically massive upper GI bleeding

### Prognosis

- risk of bleeding: 30% in first year
- risk of rebleeding: 50-70% (20% mortality at 6 wk)

**Investigations**

- endoscopy

**Management****Figure 10. Management of bleeding esophageal varices**

Not depicted: Intravenous ceftriaxone (lowers risk of sepsis, especially spontaneous bacterial peritonitis)



If varices isolated to stomach, think of splenic vein thrombosis.



Gastric varices best treated by endoscopic injection of cyanoacetate ("crazy glue").



In a prospective study of upper GI tract bleeding, mortality, recurrent bleeding, and adverse events were lower when transfusions were given only when the hemoglobin concentration fell below 70 g/L, compared to transfusions given when the hemoglobin fell below 90 g/L. The benefit was most marked in variceal bleeding with Childs-Pugh Class A or B cirrhosis (see below under cirrhosis), but also seen in peptic ulcer. Exclusion criteria included exsanguinating bleeding, acute coronary syndrome and stroke.

*N Engl J Med* 2013;368:11-21

## Mallory-Weiss Tear

**Definition**

- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

**Etiology**

- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia usually present

**Clinical Features**

- hematemesis  $\pm$  melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

**Management**

- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection  $\pm$  clips or surgical repair

## Lower Gastrointestinal Bleeding

**Definition**

- bleed distal to ligament of Treitz

**Etiology**

- rule out upper GI source
- diverticular (60% from right colon)
- vascular
  - angiodysplasia
  - anorectal (hemorrhoids, fissures)
- neoplasm
  - cancer
  - polyps
- inflammation
  - colitis (ulcerative, infectious, radiation, ischemic)
- post-polypectomy

**Clinical Features**

- hematochezia (see Figure 11)
- anemia
- occult blood in stool
- rarely melena

**Management**

- treat underlying cause



Always exclude upper GI lesion before localizing the site of the bleeding to the lower GI tract.

**Lower GI Bleed****CHAND**

Colitis [radiation, infectious, ischemic, IBD (UC > CD)]

Hemorrhoids/fissure

Angiodysplasia

Neoplastic

Diverticular disease

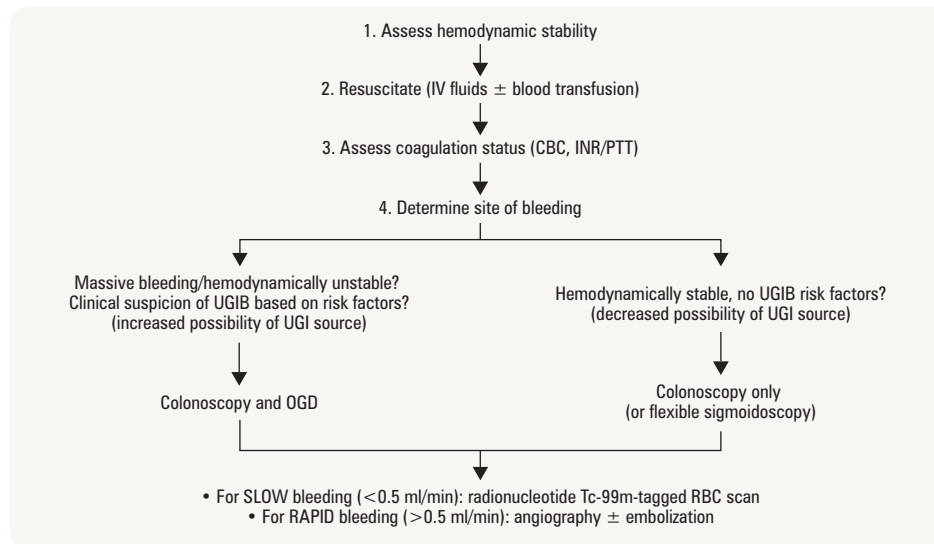


Figure 11. Approach to hematochezia

## Colorectal Carcinoma (CRC)

- see [General Surgery](#), GS34

## Colorectal Polyps

- see [General Surgery](#), GS33

## Familial Colon Cancer Syndromes

- see [General Surgery](#), GS33

## Benign Anorectal Disease

- see [General Surgery](#), GS38

## Liver

## Investigations of Hepatobiliary Disease

### A. TEST OF LIVER FUNCTION

#### Prothrombin Time (PT or INR)

- a marker of hepatic protein synthesis
- increased by:
  - impaired hepatic protein synthesis (>80%) (including all coagulation factors except VIII) i.e. hepatocellular dysfunction
  - vitamin K deficiency
  - vitamin K administration promptly corrects PT in vitamin K deficiency (malnutrition, malabsorption, etc.) but not in hepatocellular dysfunction; thus in the absence of vitamin K deficiency, PT is a reliable index of hepatocellular dysfunction

#### Serum Albumin Level

- a marker of hepatic protein synthesis; must exclude malnutrition, renal or GI losses and significant inflammatory or malignant illness of any organ system

#### Serum Bilirubin

- marker of hepatic excretion: transport from hepatocyte to bile
- canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect = unconjugated bilirubin
- liver dysfunction causes hyperbilirubinemia (elevated direct bilirubin) since conjugation preserved even in end stage liver failure



All clotting factors except factor VIII and von Willebrand factor are exclusively synthesized in the liver.



**Serum transaminases >1000 due to**

- Viral hepatitis
- Drugs
- Autoimmune hepatitis
- Hepatic ischemia
- Less often, common bile duct stone



ALT > AST = most causes of hepatitis  
AST > ALT = alcoholic liver disease or other causes of hepatitis that have progressed to advanced cirrhosis

**B. TESTS OF LIVER DAMAGE**

- disproportionately increased AST or ALT = hepatocellular damage
  - ALT more specific to liver; AST from multiple sources (especially muscle)
  - elevation of both highly suggestive of liver injury
  - most common cause of elevated ALT is fatty liver
- disproportionately increased ALP and GGT = cholestasis
  - if ALP is elevated alone, rule out bone disease by fractionating ALP
  - if ALP elevation out of proportion to ALT/AST elevation, consider:
    - obstruction of common bile duct (extraluminal = pancreatic Ca, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths)
    - destruction of microscopic ducts (e.g. PBC)
    - bile acid transporter defects (drugs, intrahepatic cholestasis of pregnancy)
    - infiltration of the liver (liver metastases, lymphoma, granulomas, amyloid)



**Alcoholic hepatitis:** history of recent alcohol, RUQ abdominal pain, AST/ALT > 2, AST usually < 300, low grade fever, mildly elevated WBC.

**Major Sources of ALP**

- Hepatobiliary tree
- Bone
- Placenta

**Acute Viral Hepatitis (General)****Definition**

- viral hepatitis lasting < 6 mo

**Clinical Features**

- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
  - nausea, vomiting, anorexia, taste/smell disturbance, headaches, fatigue, myalgia, low-grade fever
  - arthralgia and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
  - pale stools and dark urine 1-5 d prior to icteric phase
  - hepatomegaly and RUQ pain
  - splenomegaly and cervical lymphadenopathy (10-20% of cases)

**Investigations**

- AST and ALT (> 10-20x normal in hepatocellular necrosis)
- ALP and bilirubin minimally elevated
- viral serology, IgM

**Treatment**

- supportive (hydration, diet)
- indications for hospitalization: encephalopathy, coagulopathy severe vomiting, hypoglycemia

**Prognosis**

- poor prognostic indicators: comorbidities, persistently high bilirubin (> 340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia
- cholestasis (most commonly with HAV infection)

**Complications**

- hepatocellular necrosis: AST, ALT > 10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

**DDx for Hepatomegaly**

- Congestive (right heart failure, Budd-Chiari syndrome)
- Infiltrative
  - Malignant (primary, secondary, lymphoproliferative, leukemia)
  - Benign (fatty liver, cysts, hemochromatosis, extramedullary hematopoiesis, amyloid)
- Proliferative
  - Infectious (viral, tuberculosis, abscess, echinococcus)
  - Inflammatory (granulomas [sarcoid], histiocytosis X)

**DDx for Hepatitis**

- Viral infection
- Alcohol
- Drugs
- Immune-mediated
- Toxins

**Causes of Elevated Serum Transaminases in Chronic Hepatitis B**

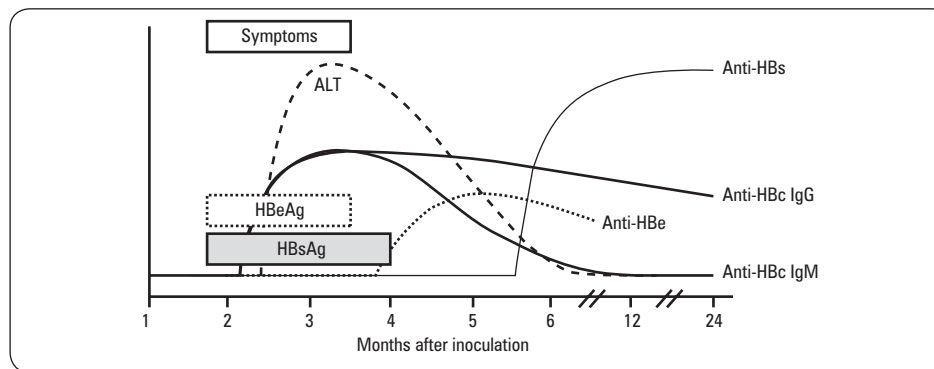
- Ongoing immune-mediated liver injury without immune control of HBV
- Reactivation from prior immune control due to lack of adequate immune control
- Seroconversion (HBeAg converting to anti-HBe; spontaneously or with Rx)
- Hepatitis D
- Liver insult (fatty liver, alcohol, drugs, hepatitis A)

**Hepatitis A Virus (HAV)**

- RNA virus
- fecal-oral transmission; incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice
- can cause fulminant hepatic failure and subsequent death (< 1-5%)
- can relapse, but never becomes chronic

**Hepatitis B Virus (HBV)****Table 14. Hepatitis B Serology**

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	Liver Enzymes
Acute HBV	+	-	+	-	IgM	
Chronic HBV (high HBV DNA)	+	-	+	-	IgG	ALT, AST elevated
Chronic HBV (low HBV DNA)	+	-	-	+	IgG	ALT, AST normal
Resolved infection	-	±	-	±	IgG	
Immunization	-	+	-	-	-	



**Figure 12. Time course of acute hepatitis B infection**

### Epidemiology

- 4 phases of chronic hepatitis B: not all will go through all 4 phases, but all will have positive HBsAg
  - immune tolerance:** extremely high HBV-DNA (>20,000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or 'incubation period' in adult with newly-acquired HBV)
  - immune clearance** (or immunoactive): falling but still elevated HBV-DNA levels (>20,000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment
  - immune control:** lower HBV-DNA (<20,000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
  - immune escape** ("core or precore mutant"): elevated HBV-DNA (>2,000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

### Management

- counselling: 40% of men and 10% of women with perinatal infection will die from HBV-related complications
- prolonged immune-mediated damage leads to higher risk of liver fibrosis
- hepatocellular carcinoma screening with ultrasound q6mo, especially if high serum HBV-DNA levels, cirrhosis, men, (age >40 in Asian men, >50 in Asian women, and >20 in African descent)
- consider pharmacological therapy if:
  - HBeAg positive + HBV-DNA >20,000 IU/mL + ALT >90; or
  - HBeAg negative + HBV-DNA >2,000 IU/mL + ALT >90 + stage ≥2 fibrosis on liver biopsy
  - treat to *prevent* flare when placed on immunosuppressive therapy such as prednisone
- treatment goal: reduce serum HBV-DNA to undetectable level
- treatment options: interferon, tenofovir, entecavir, lamivudine, adefovir
- vaccinate against HAV if serology negative (to prevent further liver damage)
- follow blood and sexual precautions

### Hepatitis D

- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with hepatitis B; causes more aggressive disease than hepatitis B virus alone
- co-infection: acquire HDV and HBV at the same time
  - better prognosis than superinfection (acute HDV infection on pre-existing HBV infection)
- HDV can present as fulminant hepatic failure (FHF) and/or accelerate progression to cirrhosis
- management: low-dose interferon (20% response) and liver transplant for end-stage disease



Risk of hepatocellular carcinoma in HBV increases with increasing age, which is likely a surrogate for increasing liver fibrosis/cirrhosis.

Risk of hepatocellular carcinoma in HCV increases only after cirrhosis develops.



Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury.



In acute hepatitis B, HDV co-infection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis.



## Hepatitis C Virus (HCV)

- RNA virus
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factor: injection drug use
- other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
- clinical manifestation develops 6-8 wk after exposure
  - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage



## Diagnosis

- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- virus genotype correlates with response to treatment but not prognosis
  - serum HCV-RNA inversely correlates with response to treatment
- normal transaminases can have underlying cirrhosis on biopsy, but otherwise excellent prognosis

## Management

- blood-borne precautions; vaccinate for hepatitis B and A if serology negative, avoid alcohol
- clearest indication for treatment is in subgroup likely to develop clinically significant liver disease
  - persistently elevated transaminases, liver biopsy shows fibrosis/cirrhosis and at least moderately severe necrosis/inflammation
- indicators of poor response to treatment: cirrhosis, genotype 1, high HCV-RNA, co-infection with HIV, African-American race
- pegylated interferon- $\alpha$  + ribavirin aims to clear HCV infection, but only 50-80% success rate and side effects common (therefore not all patients are treated)
  - “sustained remission” = undetectable HCV-RNA 6 mo off treatment (which generally means that HCV has been successfully eradicated)
  - pegylated interferon- $\alpha$  SC injection weekly and ribavirin PO bid and add proteinase inhibitor PO (bocepravir or telaprevir) for genotype 1
- length of treatment determined by time required for HCV-RNA to fall
- measure HCV-RNA at 1 and 3 mo after starting treatment
- adverse effects: depression/fatigue, hemolysis, bone marrow suppression (monitor CBC regularly), fevers/myalgia, precipitates autoimmune diseases (rare), skin rashes
- recently introduced proteinase inhibitors for genotype I (most common, least amenable to treatment) have significantly increased sustained remission rate to up to 70%



HCV treatment lowers the risk of hepatocellular carcinoma.



### Risk Factors for Progression

- EtOH
- HIV co-infection
- Old age at diagnosis

## Prognosis

- 80% of acute hepatitis C become chronic (of these 20% evolve to cirrhosis)
- risk of hepatocellular carcinoma increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

**Table 15. Characteristics of the Viral Hepatitides**

	HAV	HBV	HCV	HDV	HEV	CMV	EBV	Yellow Fever
<b>Virus Family</b>	<i>Picornaviridae</i>	<i>Hepadnaviridae</i>	<i>Flaviviridae</i>	<i>Deltaviridae</i>	<i>Caliciviridae</i>	<i>Herpesviridae</i>	<i>Herpesviridae</i>	<i>Flavivirus</i>
<b>Genome</b>	RNA	DNA	RNA	RNA	RNA	DNA	RNA	RNA
<b>Envelope</b>	No	Yes	Yes	Yes	No	Yes	Yes	Yes
<b>Transmission</b>	Fecal-oral	Parenteral/sexual or equivalent Vertical	Parenteral /sexual (transfusion, IVDU, sexual (<HBV)) 40% have no known risk factors	Non-parenteral (close contact in endemic areas) Parenteral (blood products, IVDU)-sexual transmission is inefficient	Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan)	Close contacts, most body fluids	Saliva-oral	Vector
<b>Incubation</b>	4-6 wk	6 wk-6 mo	2-26 wk	3-13 wk	2-8 wk	20-60 d	30-50 d	3-6 d
<b>Onset</b>	Usually abrupt	Usually insidious	Insidious	Usually abrupt	Usually abrupt	Variable	Variable	Usually abrupt
<b>Communicability</b>	2-3 wk in late incubation to early clinical phase Acute hepatitis in most adults, 10% of children	HBsAg + state highly communicable Increased during third trimester or early post-partum	Communicable prior to overt symptoms and throughout chronic illness	Infectious only in presence of HBV (HBsAg required for replication)	Unknown	Variable – dormant or persistent	Communicable highest during year after primary infection but never zero	Variable, vector-dependent
<b>Chronicity</b>	None, although can relapse	5% adults, 90% infants	80%, 20% of which develop cirrhosis	5%	None	Common; latent	Common; latent	Infection confers lifelong immunity
<b>Serology</b>	Anti-HAV (IgM)	See Table 15	HCV-RNA Anti-HCV (IgG/IgM)	HBsAg Anti-HDV (IgG/IgM)	Anti-HEV (IgG/IgM)	Anti- CMV (IgM/IgG)	Monospot; anti-EBV IgM/IgG, EBV DNA quantitation	Anti-YF (IgM/IgG)
<b>Immunity</b>	Yes	Yes	?	Yes	?	?	?	Yes
<b>Vaccine</b>	Havrix, 2 doses q6mo, combined with Twinrix at 0, 7, and 21 d	Recombivax HB TM, age 11-15, 2 doses q6mo	No	No	No	No	No	YF-VAX, 1 dose booster q10yr
<b>Management</b>	General hygiene Treat close contacts (anti-HAV Ig) Prophylaxis for high-risk groups (HAV vaccine $\pm$ HAV Ig) unless immune	Prevention: HBV vaccine and/or hepatitis B Ig (HBIG) for needlestick, sexual contact, infants of infected mothers unless already immune	Prevention: no vaccine Rx: IFN + ribavirin	Prevention: HBV vaccine	Prevention: general hygiene, no vaccine	In high risk transplant patients: CMV IG and anti-virals (ganciclovir, valganciclovir)	Supportive treatment post infection	Prevention Supportive treatment post infection

**Table 15. Characteristics of the Viral Hepatitis** (continued)

	HAV	HBV	HCV	HDV	HEV	CMV	EBV	Yellow Fever
<b>Acute mortality</b>	0.1-0.3%	0.5-2%	1%	2-20% coinfection with HBV, 30% superinfection Predisposes HBV carriers to more severe hepatitis and faster progression to cirrhosis	1-2% overall, 10-20% in pregnancy	Rare in immunocompetent adults	Rare	20-60% in developing countries
<b>Oncogenicity</b>	No	Yes	Yes	?	No	No	Yes	No
<b>Complications</b>	Can cause fulminant hepatic failure and subsequent death (<1-5%)	Hepatocellular carcinoma secondary to cirrhosis, Serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda	Hepatocellular carcinoma in 2-5% of cirrhosis per year, cryoglobulinemia, B-cell non-Hodgkin lymphoma	Leukocytoclastic vasculitis, membranous glomerulonephropathy	Mild, except in third trimester (10-20% fulminant liver failure)	5% of newborns with multiple handicaps Immunocompromised patients at risk of CMV-induced hepatitis, retinitis, colitis, esophagitis, pneumonitis	Associated with Burkitt's lymphoma and nasopharyngeal carcinoma (rare in Western world)	Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates

## Autoimmune Chronic Active Hepatitis

- diagnosis of exclusion: rule out viruses, drugs, metabolic or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrahepatic manifestations
  - sicca, Raynaud's, thyroiditis, Sjögren's, arthralgias
  - hypergammaglobulinemia
    - ♦ anti-smooth muscle antibody elevation is most characteristic; also elevations in anti-LKM (liver kidney microsome, especially in children)
      - less specific: elevated ANA, RF
    - ♦ can have false positive viral serology (especially anti-HCV)
    - ♦ biopsy – periportal (zone 1) and “interface” inflammation and necrosis
- management: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

## Drug-Induced Liver Disease

**Table 16. Classification of Hepatotoxins**

	Direct	Indirect
<b>Example</b>	Acetaminophen, CCl <sub>4</sub>	Phenytoin, INH
<b>Dose-dependence</b>	Usual	Unusual
<b>Latent period</b>	Hours-days	Weeks-months
<b>Host factors</b>	Not important	Very important
<b>Predictable</b>	Yes	No (idiosyncratic)



**Hy's Law:** drug-induced hepatocellular jaundice indicates a mortality of at least 10%.

### Specific Drugs

- acetaminophen
  - metabolized by hepatic cytochrome P450 system
  - can cause FHF (transaminases >1,000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite is formed → covalently binds to hepatocyte membrane
  - presentation:
    - ♦ first 24 h: nausea and vomiting (usually within 4-12 h of overdose)
    - ♦ 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - ♦ >48 h: continued hepatic necrosis possibly complicated with FHF or resolution
    - ♦ note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy:
    - ♦ gastric lavage/emesis (if <2 h after ingestion)
    - ♦ oral activated charcoal
    - ♦ N-acetylcysteine (NAC, Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given no matter when time of ingestion)
      - promotes hepatic glutathione regeneration
    - ♦ no recorded fatal outcomes if NAC given before increase in transaminases
- chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus and eosinophilia

- INH (isoniazid)
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age
- methotrexate
  - causes cirrhosis; increased risk in the presence of obesity, diabetes, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
- others: azoles, statins, methylodopa, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines
- herbs: chaparral, chinese herbs (e.g. germander, comfrey, bush tea)

## Wilson's Disease



### Definition

- autosomal recessive defect in copper metabolism (gene ATP7B)

### Pathology

- decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin

### Clinical Manifestations

- liver: acute hepatitis, fulminant liver failure, chronic active hepatitis, cirrhosis, low risk of hepatocellular carcinoma
- eyes: Kayser-Fleischer rings (copper deposits in Descemet's membrane); more common in patients with CNS involvement, present in 50% if only liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi's syndrome (proximal tubule transport defects) and stones
- blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
- joints: arthritis, bone demineralization, calcifications



#### Clinical Manifestations of Wilson's Disease

##### ABCD

##### Asterixis

Basal ganglia degeneration: suspect if parkinsonian features in the young

Ceruloplasmin ↓

##### Cirrhosis

Corneal deposits (Kayser-Fleischer ring)

Copper

Dementia

### Investigations

- suspect if increased liver enzymes with clinical manifestations at young age (<30); especially combination of liver disease with dystonia, psychiatric symptoms
- screening tests:
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion
- gold standard:
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible

### Treatment

- 4 drugs available:
  1. penicillamine chelates copper, poorly tolerated
  2. trientine chelates copper
  3. zinc impairs copper excretion in stool/ decreases copper absorption from gut
  4. tetrathiomolybdate preferred if neurological involvement
- screen relatives
- liver transplant in severe cases

## Hemochromatosis



### Definition

- excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body stores of iron increased to 20-40 g (normal 1 g)

### Etiology

- primary hemochromatosis
  - primarily due to common recessive gene (HFE, 5%); 1/400 patients are homozygotes
  - results in ongoing gut absorption of iron despite adequate iron stores
- secondary hemochromatosis
  - parenteral iron overload (e.g. transfusions)
  - chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
  - excessive iron intake



Gene mutation not 100% penetrant: so not all with homozygous gene defect have clinically significant iron overload.

### Clinical Features

- usually presents with trivial elevation in serum transaminases
- liver: cirrhosis (30%), HCC (200x increased risk) – most common cause of death (1/3 of patients)
- pancreas: diabetes, chronic pancreatitis
- skin: bronze or grey (due to melanin, not iron)
- heart: dilated cardiomyopathy
- pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
- joints: arthralgia (any joint, but especially MCP joints), chondrocalcinosis

### Investigations

- screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
  - transferrin saturation (free  $\text{Fe}^{2+}$ /TIBC) >50%
  - serum ferritin >400 ng/mL
  - HFE gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
- liver biopsy (to define degree of iron overload and to detect cirrhosis)
  - usually indicated if age >40, ALT/AST more than 2.5 times the upper limit of normal, or ferritin >1000
- HCC screening if cirrhosis

### Treatment

- phlebotomy: weekly or q2wk then lifelong maintenance phlebotomies q2-6mo
- deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

### Prognosis

- normal life expectancy if treated before the development of cirrhosis or diabetes



Ferritin may never normalize if other causes of high ferritin present (e.g. fatty liver from metabolic syndrome or alcohol).

## Alcoholic Liver Disease

### Types of Lesions

- fatty liver (all alcoholics): always reversible if alcohol stopped
- alcoholic hepatitis (35% of alcoholics): usually reversible if alcohol stopped
- cirrhosis (10-15% of alcoholics): potentially irreversible

### Pathophysiology

- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde:
  - reduces  $\text{NAD}^+$  to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- ethanol increases gut permeability leading to increased bacterial translocation
- alcohol metabolism causes:
  - relative hypoxia in liver zone III > zone I
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis:
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

### Clinical Features

- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10 to 20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not accurately predict type of liver involvement
- fatty liver:
  - mildly tender hepatomegaly; jaundice rare
  - mildly increased transaminases <5x normal
- alcoholic hepatitis:
  - variable severity: mild to fatal liver failure
  - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice and mildly elevated INR)
  - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased white blood cell count – mimics RLL pneumonia and cholecystitis



#### Standard Drink Equivalent

1 standard drink = 14 g EtOH  
 = 12 oz beer (5% alcohol)  
 = 5 oz wine (12-17%)  
 = 3 oz fortified wine (17-22%)  
 = 1.5 oz liquor (40%)

Tip: Percentage alcohol multiplied by oz roughly equals 60



#### Biopsy + Histology of Alcoholic Hepatitis (triad)

- Hepatocyte necrosis with surrounding inflammation in zone III
- Mallory bodies (intracellular eosinophilic aggregates of cytokeratins)
- Chicken-wire fibrosis (network of intralobular connective tissue surrounding cells and venules)

- blood tests are non-specific, but in general:
  - AST:ALT >2:1 (usually <300)
  - increased GGT
  - CBC: increased MCV (mean corpuscular volume), increased WBC
- prognosis: Maddrey's discriminant function (based on PT and bilirubin) predicts mortality

### Treatment

- alcohol cessation (see [Psychiatry](#), PS22)
  - Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
- multivitamin supplements (especially thiamine)
- caution with drugs metabolized by the liver
- prednisone 40 mg OD x 28 d (taper over 2-4 wk) in subgroup with elevated bilirubin and INR, or if encephalopathy; but contraindicated in GI bleeding, renal failure, infection
- pentoxifylline decreases TNF, shown in one trial to reduce death, albeit only from renal failure, favourable side-effect profile

### Prognosis

- fatty liver: complete resolution with cessation of alcohol intake
- alcoholic hepatitis mortality
  - immediate: 30%-60% in the first 6 mo if severe
  - with continued alcohol: 70% in 5 yr
  - with cessation: 30% in 5 yr



### GI Complications of Alcohol Abuse

- **Esophagus**
  - Mallory-Weiss tear
  - Esophageal varices (secondary to portal hypertension)
- **Stomach**
  - Alcoholic gastritis
- **Pancreas**
  - Acute pancreatitis
  - Chronic pancreatitis
- **Liver**
  - Alcoholic hepatitis
  - Fatty liver
  - Cirrhosis
  - Hepatic encephalopathy
  - Portal hypertension (secondary to cirrhosis)
  - Ascites (secondary to cirrhosis)
  - HCC (secondary to cirrhosis)

## Non-Alcoholic Fatty Liver Disease (NAFLD)

### Etiology/Epidemiology

- spectrum of disorders characterized by macrovesicular hepatic steatosis
- most common cause of liver disease in North America

### Pathophysiology

- pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
- changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

### Risk Factors

- likely a component of the metabolic syndrome along with type II diabetes, hypertension, hypertriglyceridemia
- rapid weight loss or weight gain

### Clinical Features/Investigations

- often asymptomatic
- may present with fatigue, malaise and vague RUQ discomfort
- elevated serum triglyceride/cholesterol levels and insulin resistance
- elevated serum AST, ALT  $\pm$  ALP; AST/ALT <1
- presents as echogenic liver texture on ultrasound
- liver biopsy diagnostic, but often necessary only for prognosis

### Management

- no proven effective therapy other than gradual weight loss
- some evidence for vitamin E (800 U daily); pioglitazone if diabetes concomitantly present
- modification of risk factors is generally recommended, especially gradual weight reduction
- optimization of therapy for diabetes, hyperlipidemia, hypertension

### Prognosis

- most die from cardiovascular or cerebrovascular disease
- better prognosis than alcoholic hepatitis
  - <25% progress to cirrhosis over a 7-10 yr period
- risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
- other clinical indicators of unfavourable prognosis: diabetes, age, metabolic syndrome

## Acute Liver Failure (ALF; Formerly Fulminant Hepatic Failure)

### Definition

- severe decline in liver function characterized by coagulation abnormality (INR > 1.5) and encephalopathy
- in setting of previously normal liver
- rapid (< 26 wk duration)

### Etiology

- drugs (especially acetaminophen), hepatitis B (measure IgM anti-HBc because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic

### Management

- correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, vigilant for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value is to exclude chronic disease, less helpful for prognosis
- liver transplant: consider early, especially if time from jaundice to encephalopathy > 7 d (e.g. not extremely rapid), age < 10 or > 40, cause is drug or unknown, bilirubin > 300  $\mu\text{mol/L}$ , INR > 3.5, creatinine > 200  $\mu\text{mol/L}$

## Cirrhosis

### Definition

- liver damage characterized by diffuse distortion of the basic architecture and replacement with scar tissue and formation of regenerative nodules
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 yr with almost normal life expectancy
- Stage 2 cirrhosis is the onset of first decompensation, typically development of ascites (most common), variceal bleeding, encephalopathy

### Etiology

- fatty liver (alcohol, metabolic syndrome)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- hemochromatosis
- $\alpha$ 1-antitrypsin deficiency
- primary biliary cirrhosis
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- idiopathic
- rare: Wilson's disease, Gaucher's disease

### Diagnosis

- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive:
  - blood work: fall in platelet count < 150 is the earliest finding, followed many yr later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event; see Figure 13)
  - FibroTest: combination of various clinical and biochemical markers that can predict degree of fibrosis
  - imaging:
    - ♦ U/S is the primary imaging modality but only finds advanced cirrhosis
    - ♦ CT to look for varices, nodular liver texture, splenomegaly, ascites
    - ♦ FibroScan: non-invasive tool using elastography (variable availability)
  - gastroscopy: varices or portal gastropathy

### Management

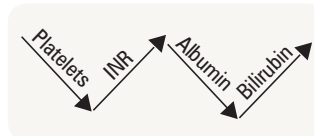
- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score (see Table 17)
- liver transplantation for end-stage disease if no alcohol for > 6 mo; use MELD stratification (see sidebar)



Fibrosis may regress and disappear if cause of liver injury is treated or resolves.



Usual causes of death in cirrhosis: renal failure (hepatorenal syndrome), sepsis, GI bleed, or HCC.



**Figure 13. Progression of liver dysfunction based on liver function tests – the “W”**



#### MELD (Model for End Stage Liver Disease)

- Predicts 3-mo survival and used to stratify patients on transplant list
- Based on creatinine, INR and total bilirubin



**Table 17. Child-Pugh Score and Interpretation**

Classification	1	2	3
Serum bilirubin ( $\mu\text{mol/L}$ )	<34	34-51	>51
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.7-2.3	>2.3
Presence of ascites	Absent	Controllable	Refractory
Encephalopathy	Absent	Minimal	Severe
Interpretation			
Points	Class	Life Expectancy	Perioperative Mortality
5-6	A	15-50 yr	10%
7-9	B	Candidate for transplant	30%
10-15	C	1-3 mo	82%
Score: 5-6 (Child's A), 7-9 (Child's B), 10-15 (Child's C)			

\*Note: Child's classification is rarely used for shunting, but is still useful to quantitate the severity of cirrhosis

## Complications

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR, thus tendency for bruising and bleeding
- variceal bleeds
  - half of patients with cirrhosis have gastroesophageal varices and one-third of these develop hemorrhage with an overall mortality of >30%
  - hepatic venous pressure gradient (HVPG)  $\geq 10$  mmHg is the strongest predictor of variceal development
  - management: resuscitation, antibiotic prophylaxis, vasoactive drugs combined with endoscopic band ligation or sclerotherapy, TIPS
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to over-diuresis)
    - acute tubular necrosis (ATN)
    - hepatorenal syndrome (HRS)
      - Type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - Type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
    - HRS can occur at any time in severe liver disease, especially after:
      - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
      - GI bleed
      - sepsis
    - treatment for hepatorenal syndrome (generally unsuccessful at improving long term survival)
      - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
      - definitive treatment is liver transplant
- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal hypertension
  - thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators vs. production of a vasodilating substance by the liver
  - clinical features:
    - hyperdynamic circulation with cardiac output  $>7$  L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency) and orthodeoxia (desaturation in the upright position, improved by recumbency)
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation



### Cirrhosis Complications

#### VARICES

Varices  
Anemia  
Renal failure  
Infection  
Coagulopathy  
Encephalopathy  
Sepsis



### Hepatorenal Syndrome vs. Pre-renal Failure – difficult to differentiate:

- Similar blood and urine findings, (see [Nephrology](#), NP33)
- Urine sodium: very low in hepatorenal; low in pre-renal
- Intravenous fluid challenge: giving volume expanders improves pre-renal failure, but not hepatorenal syndrome



### Hepatopulmonary Syndrome

#### Clinical triad:

- Liver disease
- Increased alveolar-arterial gradient while breathing room air
- Evidence for intrapulmonary vascular abnormalities

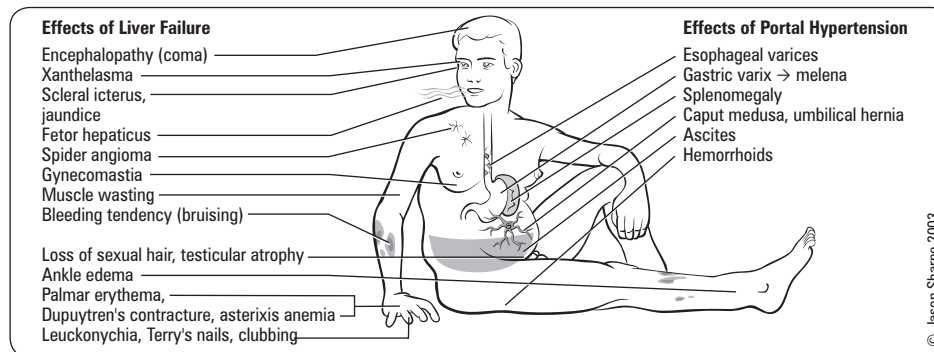


Figure 14. Clinical features of liver disease



#### Portal Hypertension

##### Signs

- Esophageal varices
- Melena
- Splenomegaly
- Ascites
- Hemorrhoids

##### Management

- $\beta$ -blockers
- Nitrates
- Shunts [e.g. transjugular intrahepatic portosystemic shunt (TIPS)]



## Hepatocellular Carcinoma (HCC)

- see [General Surgery](#), GS43

## Liver Transplantation

- see [General Surgery](#), GS44

## Portal Hypertension

### Definition

- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure)  $>5$  mmHg

### Pathophysiology

- 3 sites of increased resistance (remember pressure = flow  $\times$  resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

### Complications

- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

### Management

- non-selective  $\beta$ -blockers (propranolol, nadolol) decrease risk of bleeding from varices
- transjugular intrahepatic portosystemic shunt (TIPS): to decrease portal venous pressure
  - shunt between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute bleeding or prevent rebleeding or treat ascites
  - shunt usually remains open for  $<1$  yr
  - complications: hepatic encephalopathy, deterioration of hepatic function
  - contraindicated with severe liver dysfunction
  - most commonly used as a "bridge" to liver transplant
- other surgically created shunts (rare): portacaval, distal spleno-renal (Warren shunt)

## Hepatic Encephalopathy

### Definition

- spectrum of potentially reversible neuropsychiatric syndromes secondary to liver disease diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

### Pathophysiology

- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain

### Precipitating Factors

- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

### Stages

- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar responses
- IV: coma (response to painful stimuli only)

### Investigations

- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out:
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves

### Treatment

- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - decrease dietary protein to 50 g/d; vegetable protein is better tolerated than animal protein
  - lactulose: titrated to achieve 2 to 3 soft stools per day
    - ♦ prevents diffusion of  $\text{NH}_3$  (ammonia) from the colon into blood by lowering pH and forming non-diffusible  $\text{NH}_4$  (ammonium)
    - ♦ serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - ♦ also acts as a laxative to eliminate nitrogen-producing bacteria from colon
- if inadequate response with lactulose may try antibiotics
  - broad-spectrum antibiotics (metronidazole, rifaximin) eliminate ammonia producing bacteria from bowel lumen
  - non-absorbable antibiotic rifaximin probably most effective treatment but only available through special access in Canada
- best acute treatment in comatose patient is tap water or lactulose enemas



#### Precipitating Factors for Hepatic Encephalopathy

##### HEPATICS

Hemorrhage in GI tract/Hypokalemia  
Excess dietary protein  
Paracentesis  
Alkalosis/Anemia  
Trauma  
Infection  
Colon surgery  
Sedatives

## Ascites



### Definition

- accumulation of excess fluid in the peritoneal cavity

### Etiology

**Table 18. Serum-Ascites Albumin Gradient as an Indicator of the Causes of Ascites**

Serum [Alb] – Ascitic [Alb] >11 g/L (1.1 g/dL) Portal Hypertension Related	Serum [Alb] – Ascitic [Alb] <11 g/L (1.1 g/dL) Non-portal Hypertension Related
Cirrhosis/severe hepatitis	Peritoneal carcinomatosis
Chronic hepatic congestion (right heart failure, Budd-Chiari)	TB
Massive liver metastases	Pancreatic disease
Myxedema	Serositis
	Nephrotic syndrome*

\* In nephrotic syndrome: decreased serum [Alb] to begin with therefore gradient not helpful



Secondary bacterial peritonitis (as opposed to primary bacterial peritonitis) usually results from a perforated viscus or surgical manipulation.

### Pathogenesis

- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis: first step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney
  - overflow hypothesis: cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily
  - peripheral arterial vasodilation theory (most popular): as portal hypertension develops in cirrhosis, production of local mediators such as nitric oxide lead to splanchnic arterial vasodilation which ultimately results in reduction of effective arterial volume and compensatory sodium and fluid retention by the kidneys (i.e. circulation volume is increased, as per overflow hypothesis, but relatively underfilled, as per underfill hypothesis)



#### Serum Ascites Albumin Gradient

- >11 g/L portal HTN
- <11 g/L unrelated to portal HTN

## Diagnosis

- abdominal ultrasound
- physical exam (clinically detectable when >500 mL):
  - bulging flanks, shifting dullness, fluid-wave test positive
  - most sensitive symptom: ankle swelling

## Investigations

- diagnostic paracentesis
  - 1<sup>st</sup> aliquot: cells and differential
  - 2<sup>nd</sup> aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis, TG if turbid and suspect chylous ascites)
  - 3<sup>rd</sup> aliquot: C&S, Gram stain
  - 4<sup>th</sup> aliquot: cytology (usually positive in peritoneal carcinomatosis)

## Treatment

- non-refractory ascites:
  - Na<sup>+</sup> restriction (daily sodium intake <2 g)
  - diuretics: spironolactone, furosemide
  - aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - double diuretic dose every 2-4 wk to achieve weight loss target
- refractory ascites (treatment with diuretics are inadequate or not tolerated):
  - therapeutic/palliative paracentesis indicated
  - IV albumin (not indicated if <5 L removed by paracentesis)
  - TIPS usually provides temporary benefit in controlling ascites but no survival advantage
  - liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis are associated with 50% 2-yr mortality

## Complication: Primary/Spontaneous Bacterial Peritonitis (SBP)

- primary/spontaneous bacterial peritonitis (SBP)
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: *E. coli* (most common), *Streptococcus*, *Klebsiella*
- diagnosis
  - absolute neutrophil count in peritoneal fluid >0.25x10<sup>9</sup> cells/L (250 cells/mm<sup>3</sup>)
  - Gram stain positive in only 10-50% of patients
  - culture positive in <80% of patients (not needed for diagnosis)
- prophylaxis: consider in patients with
  - cirrhosis or GI bleed: IV ceftriaxone daily or norfloxacin bid x 7 d
  - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
- treatment
  - IV antibiotics (cefotaxime 2 g IV q8h is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
  - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure



### Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis

*Gastroenterology* 2007;133:818-824

**Study:** RCT, double-blinded study with 1 yr follow-up.

**Population:** 68 patients with cirrhosis, ascites, ascitic fluid protein <15 g/L and impaired renal function or severe liver failure.

**Intervention:** General, regional or combined anesthesia to patients undergoing a surgical procedure.

**Main Outcome:** Norfloxacin versus placebo.

**Results:** There was a significant reduction of patients developing spontaneous bacterial peritonitis (SBP) (6% vs. 30%,  $p=0.02$ ) and spontaneous bacteremia (0% vs. 12%,  $p=0.05$ ) with norfloxacin therapy. There were significantly fewer patients who developed all-cause renal failure (7 vs. 16,  $p=0.03$ ) and hepatorenal syndrome (HRS) with norfloxacin therapy. Probability of survival at 3 mo (94% vs. 62%,  $p=0.02$ ) and 1 yr (60% vs. 48%,  $p=0.003$ ) were high in patients treated with norfloxacin.

**Conclusion:** Primary prophylaxis with norfloxacin in patients with advanced cirrhosis reduced SBP, HRS, and improved 1 yr survival.

# Biliary Tract



## Jaundice

- see Table 2, Figures 15 and 16

## Signs and Symptoms

- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic tumour (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer, although most patients with pancreatic cancer have pain
- kernicterus: rarely seen in adults due to maturation of blood brain barrier

## Investigations

- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
- U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
- direct bile duct visualization
  - magnetic resonance cholangiopancreatography (MRCP): non-invasive
  - endoscopic ultrasound (EUS): sensitive for stones and pancreatic tumours
  - endoscopic retrograde cholangiopancreatography (ERCP): invasive, most accurate, allows for therapeutic intervention
  - percutaneous transhepatic cholangiography (PTC): if ERCP fails, if obstruction is in liver

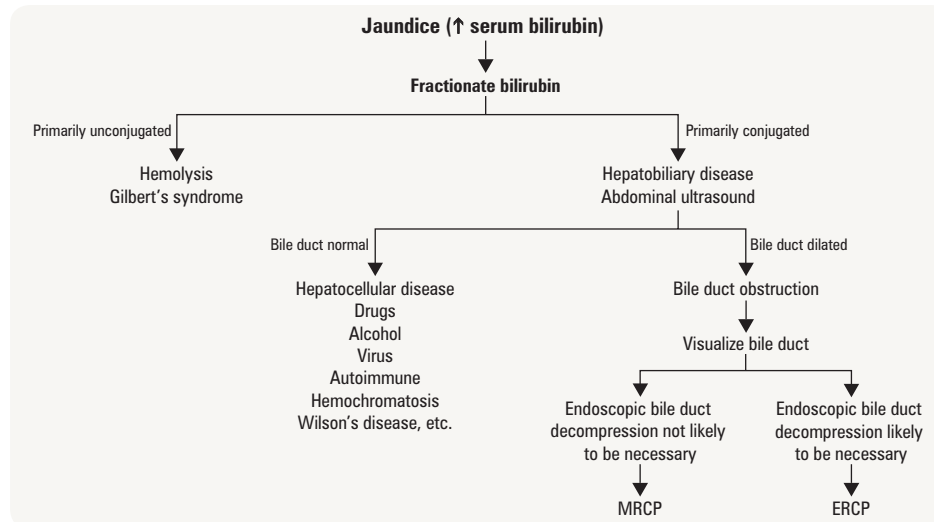


Figure 16. Approach to jaundice

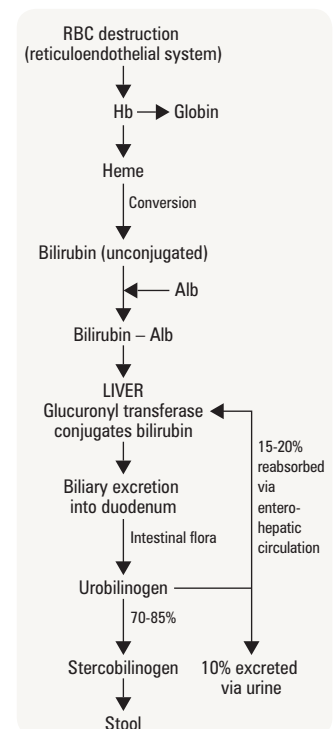


Figure 15. Production and excretion of bilirubin

## Gilbert's Syndrome

### Definition

- mild decrease in glucuronyltransferase activity leading to defective conjugation of bilirubin

### Etiology/Epidemiology

- some patients have decreased hepatobiliary uptake
- affects 7% of population, especially males
- autosomal dominant, 70% due to a mutation in the UGT gene

### Signs and Symptoms

- presents in teens-20s, often an incidental finding
- only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting; no other clinical implications

### Treatment

- none indicated (entirely benign)



### Gilbert's Syndrome vs. Crigler-Najjar Syndrome

**Gilbert's Syndrome:** mild decrease in glucuronyltransferase activity.

**Crigler-Najjar Syndrome:** complete deficiency of glucuronyltransferase.

## Sclerosing Cholangitis

### Definition

- inflammation of biliary tree (intra and/or extrahepatic bile ducts) leading to scarring and lumen obliteration

### Etiology

- primary/idiopathic (most common)
  - associated with IBD, more commonly UC, in up to 70% of patients (usually male)
  - one of the most common indications for transplant
- secondary (less common)
  - long-term choledocholithiasis
  - cholangiocarcinoma
  - surgical/traumatic injury (iatrogenic)
  - contiguous inflammatory process
  - post-ERCP
  - associated with HIV/AIDS ("HIV cholangiopathy")

**Signs and Symptoms**

- often insidious, may present with fatigue and pruritus
- may present with signs of episodic bacterial cholangitis secondary to biliary obstruction

**Diagnosis**

- increased ALP (hallmark), less often increased bilirubin
- mildly increased AST, usually <300 U/L
- p-ANCA (30-80%), elevated IgM (40-50%)
- ERCP shows narrowing and dilatations of bile ducts that may result in “beading”, both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC

**ERCP**

- Absence of narrowing in PBC
- Narrowing of intra and extrahepatic ducts in PSC

**Complications**

- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat

**Management**

- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma
- endoscopic sphincterotomy, biliary stent in selected cases of dominant CBD stricture
- antibiotics for cholangitis
- suppurative cholangitis requires emergency drainage of pus in CBD
- liver transplantation appears the best treatment for advanced sclerosing cholangitis (nearly 90% 1-yr survival; mean follow-up from time of diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that at least in high doses it increases mortality

**Prognosis**

- unfavourable regardless of treatment
- mean survival after diagnosis remains 4-10 yr

## Primary Biliary Cirrhosis (PBC)

**Definition**

- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

**Etiology/Epidemiology**

- likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome, RA, thyroiditis)
- affects mainly middle-aged women (M:F = 1:9)

**Signs and Symptoms**

- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal hypertension, ascites
- high incidence of osteoporosis

**Investigations**

- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  - may have: xanthelasmas, xanthomas
- liver biopsy confirms diagnosis and stages severity
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- recently described “overlap” syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis

**Clinical Course**

- can be fatal, although not all asymptomatic patients show progression

**Treatment**

- treat with ursodiol (less frequently colchicine, methotrexate)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- monitor for thyroid disease
- liver transplant if disease severe, progressive



Table 19. Primary Sclerosing Cholangitis vs. Primary Biliary Cirrhosis

	Primary Sclerosing Cholangitis	Primary Biliary Cirrhosis
<b>Predominant gender</b>	Male	Female
<b>Associated comorbidities</b>	IBD, especially UC	Other autoimmune disorders (Sjögren's, CREST, RA)
<b>Affected ducts</b>	Both intra- and extra-hepatic	Intrahepatic only
<b>Investigations</b>	ERCP/MRCP (narrowing and dilatations of ducts visualized)	Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)

## Secondary Biliary Cirrhosis

### Definition

- cirrhosis from prolonged partial or total obstruction of major bile ducts

### Etiology

- acquired: post-op strictures, chronic pancreatitis, sclerosing cholangitis, stone in bile duct
- congenital: cystic fibrosis (CF), congenital biliary atresia, choledochal cysts

### Diagnosis

- cholangiography and liver biopsy

### Treatment

- treat obstruction, give antibiotics for cholangitis prophylaxis

## Biliary Colic, Cholecystitis

- see [General Surgery](#), GS46



## Ascending Cholangitis

- see [General Surgery](#), GS48



### Definition

- infection of the biliary tree

### Etiology

- stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
- infection originates in the duodenum or spreads hematogenously from the portal vein
- bacteria
  - *E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*
  - co-infection with *Bacteroides* and *Clostridia* can occur

### Signs and Symptoms

- Charcot's triad: fever, RUQ pain, jaundice (50-70%)
- Reynold's Pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

### Diagnosis

- increased WBC
- usually increased ALP and bilirubin, ALT variably elevated
- blood culture
- abdominal U/S: CBD dilation, stones

### Treatment

- most important is drainage, ideally via ERCP, but if necessary by percutaneous biliary or surgical routes
- antibiotic therapy: broad spectrum to cover Gram-negatives, *Enterococcus*, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

### Prognosis

- good with effective drainage and antibiotics in mild to moderate cases
- high mortality (~50%) in patients with Reynold's Pentad



#### Charcot's Triad

- RUQ pain
- Fever
- Jaundice



#### Reynold's Pentad

- Charcot's triad
- Hypotension
- Altered mental status

# Pancreas

## Pancreatic Enzyme Abnormalities

### Causes of Increased Serum Amylase

- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

### Causes of Increased Serum Lipase

- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure



#### Pancreatic Enzymes

**TALC**  
 Trypsin  
 Amylase  
 Lipase  
 Chymotrypsin



When serum amylase >5x normal, the cause is almost always pancreatitis or renal disease.



## Acute Pancreatitis

### Etiology

Idiopathic: thought to be hypertensive sphincter or microlithiasis

Gallstones (45%)

Ethanol (35%)

Tumours: pancreas, ampulla, choledochocoele

Scorpion stings

Microbiological

- bacterial: *Mycoplasma*, *Campylobacter*, TB, *M. avium intracellulare*, *Legionella*, leptospirosis
- viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
- parasites: ascariasis, clonorchiasis, echinococcosis

Autoimmune: SLE, polyarteritis nodosa (PAN), Crohn's

Surgery/trauma

- manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer

Hyperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), Hypercalcemia, Hypothermia

Emboli or ischemia

Drugs/toxins

- azathioprine, mercaptopurine, furosemide, estrogens, methyl dopa, H<sub>2</sub>-blockers, valproic acid, antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)



When thinking about the causes of acute pancreatitis remember: **I GET SMASHED**, but vast majority due to gallstones or ethanol

### Pathogenesis

- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
- in ethanol-related pancreatitis, pathogenesis is unknown
- in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in SPINK 1 gene which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

### Pathology

- mild (interstitial)
  - peri-pancreatic fat necrosis
  - interstitial edema
- severe (necrotic)
  - extensive peri-pancreatic and intra-pancreatic fat necrosis
  - parenchymal necrosis and hemorrhage → infection in 60%
  - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- severity of clinical features may not always correlate with pathology

- 3 phases:
  - local inflammation + necrosis → hypovolemia
  - systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  - local complications 2 wk after presentation → pancreatic sepsis/abscess

### Signs and Symptoms

- pain: epigastric, noncolicky, constant
- can radiate to back
- may improve when leaning forward (Inglefinger's sign)
- tender rigid abdomen; guarding
- nausea and vomiting
- abdominal distention from paralytic ileus
- fever: chemical, not due to infection
- jaundice: compression or obstruction of bile duct
- Cullen's/Grey-Turner's signs
- tetany: transient hypocalcemia
- hypovolemic shock: can lead to renal failure
- acute respiratory distress syndrome
- coma

### Investigations

- increased serum pancreatic enzymes: amylase, lipase (more specific)
- ALT >150 specific for biliary cause
- increased WBC, glucose, low calcium
- imaging: CT most useful for diagnosis and prognosis
  - x-ray: "sentinel loop" (dilated proximal jejunum), calcification and "colon cut-off sign" (colonic spasm)
  - U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  - CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  - ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

### Prognosis

- usually a benign, self-limiting course, single or recurrent
- occasionally severe leading to:
  - shock
  - pulmonary edema
  - multi-organ dysfunction syndrome
  - GI ulceration due to stress
  - death
- mortality according to Ranson's criteria (see sidebar)
  - ≤2 criteria = <5% mortality
  - 3-4 criteria = 15-20%
  - 5-6 criteria = 40%
  - ≥7 criteria = >99%
  - multiple other prognostic indices available, more accurate than Ranson but difficult to remember (e.g. APACHE)

### Treatment

- goals (only supportive therapy available):
  - (1) hemodynamic stability
  - (2) analgesia
  - (3) oxygen
  - (4) stop progression of damage (difficult)
  - (5) treat local and systemic complications
- antibiotics controversial except in documented infection (use cephalosporins, imipenem)
- aspirate necrotic areas of pancreas to diagnose infection; drain if infected
- IV fluids (crystalloid or colloid)
  - beware third spacing of fluid, monitor urine output carefully
- NG suction (rests pancreas) if vomiting, stomach very dilated
- endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
- nutritional support: nasojejunal feeding tube or TPN if cannot tolerate enteric feeds
  - recent evidence supports nasogastric enteral (or oral if feasible) feeds
- no benefit: glucagon, atropine, aprotinin, H<sub>2</sub>-blockers, peritoneal lavage
- follow clinically and CT/ultrasound to exclude complications
- chief role of surgery is to drain fluid or excise necrotic tissue (necrosectomy) in the case of infected pancreatic necrosis (try to delay for >2 wk to allow demarcation between viable and necrotic tissue)



#### Cullen's Sign

Periumbilical ecchymosis

#### Grey-Turner's Sign

Flank ecchymosis



#### Increased Amylase

- Sensitive, not specific

#### Increased Lipase

- Higher sensitivity and specificity
- Stays elevated longer



#### Ranson's Criteria: Prognostic Indicator of Mortality in Pancreatitis not due to Gallstones

##### At Admission

**G:** Blood Glucose >11 mmol/L (>200 mg/dL) (with no history of hyperglycemia)

**A:** Age >55

**L:** Serum LDH >350 IU/L

**A:** AST >250 IU/L

**W:** WBC >16 x 10<sup>9</sup>/L (16,000/mm<sup>3</sup>)

##### During First 48 h

**C:** Serum Calcium <2 mmol/L (<8 mEq/L)

**H:** Hematocrit drop >10%

**O:** Arterial PO<sub>2</sub> <60 mmHg

**B:** Base deficit >4 mmol/L (>4 mEq/L)

**B:** BUN rise >1.8 mmol/L (>5 mg/dL)

**S:** Estimated fluid Sequestration >6 L

- Difficult course if 2 criteria present
- High mortality if ≥3 criteria present



#### Prophylactic Antibiotics Cannot Reduce Infected Pancreatic Necrosis and Mortality in Acute Necrotizing Pancreatitis: Evidence from a Meta-analysis of Randomized Controlled Trials

*Am J Gastroenterol* 2008;103:104-110

**Purpose:** To review the effectiveness of IV antibiotics on pancreatic necrosis.

**Study Selection:** RCTs comparing antibiotics with placebo or no treatment.

**Results:** Seven trials (n= 467) were included. Antibiotics were not statistically superior to controls in reduction of infected necrosis and mortality.

**Conclusion:** Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in patients with acute necrotizing pancreatitis.

**Note:** In practice the temptation to give antibiotics for pancreatitis is mainly in the setting of a sick patient with fever and suggestive pancreatic necrosis on CT scan. It is difficult to determine whether pancreatic necrosis has become infected without aspiration biopsy. See *Curr Gastroenterol Rep* 2009;11:104-110

**Late Complications**

- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  - drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
- infected necrosis/abscesses: antibiotics + percutaneous drainage, endoscopic vs. surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: diabetes, pancreatic duct damage

## Chronic Pancreatitis

**Definition**

- irreversible damage to pancreas characterized by:
  - (1) pancreatic cell loss (from necrosis)
  - (2) inflammation
  - (3) fibrosis

**Etiology/Pathophysiology**

- alcohol (most common):
  - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
  - changes composition of pancreatic juice (e.g. increases viscosity)
  - decreases pancreatic secretion of pancreatic stone protein (lithostathine) which normally solubilizes calcium salts
    - ♦ precipitation of calcium within pancreatic duct results in duct and gland destruction
  - toxic effect on acinar and duct cells – directly or via increasing free radicals
  - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
  - varying degrees of ductular dilatation, strictures, protein plugs, calcification
  - no satisfactory theory to explain why only a minority of alcoholics develop pancreatitis
- unusual causes
  - cystic fibrosis
  - severe protein-calorie malnutrition
  - hereditary
  - idiopathic

**Signs and Symptoms**

- early stages:
  - recurrent attacks of severe abdominal pain (upper abdomen and back)
  - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
  - malabsorption syndrome when >90% of function is lost, steatorrhea
  - diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed

**Investigations**

- laboratory:
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
- AXR: looking for pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts
- 72-h fecal fat test: measures exocrine function
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
- fecal pancreatic enzyme measurement (elastase-1, chymotrypsin) available only in selected centres

**Management**

- most common problem is pain, difficult to control
- general management:
  - total abstinence from alcohol
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas “burns out”
- endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct



Gallstones only cause acute pancreatitis (not chronic pancreatitis).

**Symptoms of Chronic Pancreatitis**

- Abdominal pain
- Diabetes
- Steatorrhea

**Etiology** = Almost Always Alcohol

**Treatment**

- Alcohol abstinence
- Pancreatic enzyme replacement
- Analgesics
- Pancreatic resection if ductular blockage

- surgery: drain pancreatic duct (pancreaticojejunostomy) if duct dilated (more effective than endoscopy); resect pancreas if duct contracted
- steatorrhea:
  - pancreatic enzyme replacement
  - restrict fat, increase carbohydrate and protein (may also decrease pain)
  - neither endoscopy nor surgery can improve pancreatic function

## Autoimmune Pancreatitis

- most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice  $\pm$  abdominal pain)

### Investigations

- histology: lymphocyte and plasma cell infiltration of pancreas
- imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage shaped, low density rim around pancreas
- serology: increased serum IgG4
- other organs involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

### Treatment

- responds to prednisone

## Clinical Nutrition

### Determination of Nutritional Status

- corrected weight loss [expressed as body mass index ( $\text{kg}/\text{m}^2$ )] is most important parameter in assessing need for nutritional support

### Investigations

- plasma proteins: albumin, pre-albumin (shorter half life than albumin), transferrin
  - decrease may indicate decreased nutritional status or disease state
- thyroid-binding globulin, retinol-binding protein (may be too sensitive)
- anthropometry (e.g. triceps skinfold thickness), grip strength less often used

Table 20. Areas of Absorption of Nutrients

	Fe	CHO	Proteins, Lipids Na <sup>+</sup> , H <sub>2</sub> O	Bile Acids	Vit B <sub>12</sub>
Duodenum	+++	+++	+++	+	
Jejunum	+	+	++	+	+
Ileum	+	+	++	+++	+++



Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection.



#### Most Common Indications for Artificial Nutrition Support include:

- Preexisting nutritional deprivation
- Anticipated or actual inadequate energy intake by mouth
- Significant multiorgan system disease

## Enteral Nutrition (EN)

### Definition

- enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
- choice of tubes: nasogastric (NG), nasojejunal (NJ), percutaneous endoscopic gastrostomy (G-tube), percutaneous endoscopic jejunostomy (J-tube) or tubes can be placed radiologically, surgically

### Indications

- oral feeding inadequate or contraindicated

### Feeds

- polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fibre
- elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolality)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

### Relative Contraindications

- non-functioning gut (e.g. intestinal obstruction, enteroenteral or enterocutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding

## Complications

- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)

## Enteral Nutrition Advantages over Parenteral Nutrition

- far fewer serious complications (especially sepsis)
- nutritional requirements for enterally administered nutrition better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- prevents gallstones by stimulating gallbladder motility
- much less expensive



### Enteral versus Parenteral Nutrition for Acute Pancreatitis

*Cochrane DB of Syst Rev* 2010;1:CD002837

**Purpose:** Compare EN versus TPN on mortality, morbidity and hospital stay in patients with pancreatitis.

**Study Selection:** RCTs of TPN versus EN in pancreatitis.

**Results:** Eight trials (n=348) were included. Enteral nutrition decreases RR of death (0.50), multiple organ failure (0.55), infection (0.39) and other local complications (0.70). It also decreased hospital stay by 2.37 d.

**Conclusion:** EN reduces mortality, organ failure, infections and length of hospital stay in patients with pancreatitis.

## Parenteral Nutrition (PN)

### Definition

- parenteral nutrition is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

### Indications

- short term (<1 mo)
  - whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively and difficult to control sepsis
  - preoperative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)
  - some evidence for efficacy, but convincing data not available for:
    - ♦ radiation/chemotherapy-induced enteritis
    - ♦ AIDS with wasting diarrhea
    - ♦ severe acute pancreatitis
- long term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of bowel (e.g. bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

### Relative Contraindications

- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem
- unreliable patient or clinical setting

### Complications of PN

- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: CHF, hyperglycemia, gallstones, cholestasis



Whenever possible, enteral nutrition is ALWAYS preferable over parenteral nutrition!



## Common Medications

**Table 21. Common Drugs Prescribed in Gastroenterology**

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
<b>Proton Pump Inhibitors</b> (H <sup>+</sup> /K <sup>+</sup> -ATPase inhibitors)	omeprazole	Losec®/Prilosec®	20 mg PO OD	Inhibits gastric enzymes H <sup>+</sup> /K <sup>+</sup> -ATPase (proton pump)	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of <i>H. pylori</i> (combined with antibiotics)	Hypersensitivity to drug	Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)
	lansoprazole or dexlansoprazole	Prevacid® Kapidex®	Oral therapy: 15-30 mg OD (before breakfast) IV therapy: 30 mg OD	Same as above	Same as above	Same as above	Same as above
	pantoprazole	Pantoloc® Protonix®	40 mg PO OD for UGIB: 80 mg IV bolus then 8 mg/h infusion	Same as above	Same as above and UGIB	Same as above	Same as above
	rabeprazole	Pariet®/Aciphex®	40 mg PO OD	Same as above	Same as above	Same as above	Same as above
	esomeprazole	Nexium®	20-40 mg PO OD	Same as above	Same as above	Same as above	Same as above
<b>Histamine H<sub>2</sub>-receptor Antagonists</b>	ranitidine	Zantac®	300 mg PO OD or 150 mg bid  IV therapy: 50 mg q8h (but tachyphylaxis a problem)	Inhibits gastric histamine H <sub>2</sub> -receptors	Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD, Zollinger-Ellison syndrome	Hypersensitivity to drug	Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression
	famotidine	Pepcid®	Oral therapy: duodenal/gastric ulcers: 40 mg qhs GERD: 20 mg bid IV therapy: 20 mg bid	Same as above	Same as above	Same as above	Same as above
<b>Stool Softener</b>	docusate sodium	Colace®	100-400 mg daily, divided in 1-4 doses	Promotes incorporation of water into stool	Relief of constipation	Presence of abdominal pain, fever, nausea and vomiting	Throat irritation, abdominal cramps, rashes
<b>Osmotic Laxatives</b>	lactulose	Lactulose/ Constulose®	Constipation: 15-30 mL OD to bid Encephalopathy: 15-30 mL bid to qid	Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid into colon, increased osmotic colonic contents, increases stool volume	Chronic constipation, prevention and treatment of portal-systemic encephalopathy	Patients who require a low galactose diet	Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage
	PEG3350	Lax-a-day®/ Golytely®	Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD	Osmotic agent causes water retention in stool and promotes frequency of stool	Relief of constipation Colonoscopy prep	Hypersensitivity to drug	Abdominal distension, pain, anal pain, thirst, nausea, rigor, tonic-clonic seizures (rare)
<b>Prokinetic Laxatives</b>	senna	Senokot®	Tablets: 1-4 PO qhs Syrup: 10-15 mL PO qhs	Induce peristalsis in lower colon	Constipation	Patients with acute abdomen	Abdominal cramps, discolouration of breast milk, urine, feces, melanosis coli and atonic colon from prolonged use (controversial)
	bisacodyl	Bisacodyl®	5-30 mg PO OD (start at 10 mg for bowel preparation)	Enteric nerve stimulation and local contact-induced secretory effects. Colonic movements	Constipation Preparation of bowel for procedure	GI obstruction Gastroenteritis	Abdominal colic, abdominal discomfort, proctitis (with suppository use), diarrhea
	metoclopramide	Maxeran®	See anti-emetics	See anti-emetics	See anti-emetics	See anti-emetics	See anti-emetics
<b>Bulk Laxatives</b>	psyllium	Metamucil®	2-6 tabs (1 tab = 0.52 g) PO qd-tid prn	Increases stool bulk → water retention in stool	Constipation	Hypersensitivity to drug GI obstruction	GI obstruction, diarrhea, constipation, abdominal cramps

**Table 21. Common Drugs Prescribed in Gastroenterology** (continued)

Class	Generic Drug Name	Trade Name	Dosing	Mechanism of Action	Indications	Contraindications	Side Effects
<b>Antidiarrheal Agents</b>	loperamide	Imodium®	Acute diarrhea: 4 mg PO initially, followed by 2 mg after each unformed stool	Acts as antidiarrheal via cholinergic, oncholingeric, opiate and nonopiate receptor-mediated mechanisms; decreases activity of myenteric plexus	Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies and other intestinal resections	Children <2 yr, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute ulcerative colitis or pseudomembranous colitis associated with broad-spectrum antibiotics	Abdominal pain or discomfort, drowsiness or dizziness, tiredness, dry mouth, nausea and vomiting, hypersensitivity reaction
	diphenoxylate/atropine	Lomotil®	5 mg PO tid to qid	Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time	Adjunctive therapy for diarrhea, as above	Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhea caused by enterotoxin producing bacteria	Dizziness, drowsiness, insomnia, headache, nausea, vomiting, cramps, allergic reaction
<b>Anti-emetics</b>	dimenhydrinate	Gravol®	25-50 mg PO/IV/IM q4-6h prn	Competitive H <sub>1</sub> receptor antagonist in GI tract, blood vessels, and respiratory tract. Blocks chemoreceptor trigger zone. Diminishes vestibular stimulation and disrupts labyrinthine function through central anticholinergic action	Motion sickness, radiation sickness, postoperative vomiting, and drug-induced nausea and vomiting	Hypersensitivity to drug	Xerostomia, sedation
	prochlorperazine	Stemetil®	5-10 mg PO/IV/IM bid-td pm	D <sub>1</sub> , D <sub>2</sub> receptor antagonist in chemoreceptor trigger zone and α adrenergic and anticholinergic effects. Depresses RAS affecting emesis	Post op nausea and vomiting, antipsychotic, anxiety	Hypersensitivity to drug	Dystonia, EPS, seizure, neuroleptic malignant syndrome (NMS) (rarely)
	metoclopramide	Maxeran®	10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs)	Dopamine and HT receptor antagonist in chemoreceptor trigger zone. Enhances response to Ach in upper GI tract, enhancing motility and gastric emptying. Increases LES tone	GER, diabetic gastroparesis, post op and chemotherapy induced nausea and vomiting, migraines, constipation	Hypersensitivity to drug, GI obstruction, perforation, hemorrhage, pheochromocytoma, seizures and EPS	Restlessness, drowsiness, dizziness, fatigue, EPS, some rare serious side effects include NMS, agranulocytosis
	ondansetron	Zofran®	Depends on procedure, generally 8-16 mg PO	Selective 5HT <sub>3</sub> receptor antagonist in central chemoreceptor trigger zone and peripherally on vagus nerve	Nausea and vomiting caused by cancer chemotherapy and radiation therapy. Multiple off label uses, including gastroenteritis nausea and vomiting	Morphine, hypersensitivity to drug	Constipation, diarrhea, increased liver enzymes, headache, fatigue, malaise, cardiac dysrhythmia
	granisetron	Kytril®	1 mg PO bid (for nausea from chemotherapy/radiation)	Same as above	Nausea and vomiting caused by cancer chemotherapy and radiation therapy	Same as above	Constipation, prolonged QT interval (rarely)
<b>IBD Agents</b>	mesalamine	Pentasa® Salofalk® Asacol® Mesasal®	CD: 1g tid/qid Active UC: 1g qid Maintenance UC: 1.6 g divided doses daily also as suppositories and enemas	5-ASA: Blocks arachidonic acid metabolism to prostaglandins and leukotrienes	IBD	Hypersensitivity to mesalamine salicylates	Abdominal pain, constipation, arthralgia, headache
	sulfasalazine	Salazopyrin®	3-4 g/d in divided doses	Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component	Colonic disease	Hypersensitivity to sulfasalazine, sulfa drugs, salicylates; intestinal or urinary obstruction, porphyria	Rash, loss of appetite, nausea, vomiting, headache, oligospermia (reversible)
	prednisone		20-40 mg PO OD for acute exacerbation	Anti-inflammatory	Mod-severe CD and UC		Complications of steroid therapy
<b>Immuno-suppressive Agents</b>	6-mercaptopurine (6-MP)	Purinethol®	CD: 1.5 mg/kg/d	Immunosuppressive	IBD: active inflammation and to maintain remission	Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hypersensitivity to azathioprine, pregnancy	Pancreatitis, bone marrow suppression, increased risk of cancer
	azathioprine	Azasan® Imuran®	IBD: 2-3 mg/kg/d	Same as above	Same as above	Same as above	Same as above
<b>Immunomodulators</b>	infliximab	Remicade®	5-10 mg/kg IV over 2 h	Antibody to TNFα	Medically refractory CD	Heart failure, moderate to severe, doses >5 mg/kg	Reported cases of reactivated TB, PCP, lymphoma, other infections

## Landmark Gastroenterology Trials

Trial	Reference	Results
ALF	<i>Gastroenterology</i> 2009; 137:856-64	IV NAC was shown to improve transplant-free survival in patients with early non-acetaminophen related acute liver failure. Later stage disease did not improve with IV NAC
BISAP	<i>Am J Gastro</i> 2009; 104:966	Five point scoring system for patients with acute pancreatitis to identify those at increased risk for mortality
Early combined vs. conventional management in Crohn's	<i>Lancet</i> 2008; 371:660-7	Initiation of more intensive therapy early in Crohn's disease may be more likely to result in corticosteroid-free remission than conventional therapy
FAMOUS	<i>Lancet</i> 2009; 374:119-25	Famotidine was effective in preventing gastric and duodenal ulcers, and erosive esophagitis in patients receiving low-dose ASA therapy
Glucocorticoids and NAC in Alcoholic Hepatitis	<i>NEJM</i> 2011; 365:1781-9	Combination therapy improved 1 mo survival, but not 6 mo survival compared to prednisolone monotherapy
MELD	<i>Gastroenterology</i> 2003; 124:91-6	MELD score can be applied for allocation of donor livers as it accurately predicts 3 mo mortality in patients with chronic liver failure
SONIC	<i>NEJM</i> 2010; 362:1383-95	In moderate-severe Crohn's disease, infliximab + azathioprine was more likely to result in corticosteroid-free remission than infliximab monotherapy. Infliximab monotherapy was more effective than azathioprine monotherapy

## References

### Atlas

Kandel G. Division of gastroenterology, St. Michael's Hospital, Toronto.  
 Olscamp G. Division of gastroenterology, St. Michael's Hospital, Toronto.  
 Saibil F. Division of gastroenterology, SWCHSC.  
 Haber G. Division of gastroenterology, Lennox Hall Hospital, New York.

### Esophageal and Gastric Disease

Devault KR, Castell DO. Guidelines for the diagnoses and treatment of gastroesophageal reflux disease. *Arch Intern Med* 1995;115:2165-2173.  
 DiPalma JA. Management of severe gastroesophageal reflux disease. *J Clin Gastroenterol* 2001;32:19-26.  
 Sharma P, Sarin SK. Improved survival with the patients with variceal bleed. *Int J Hepatol* 2011; Epub 2011 Jul 7.  
 Verbeek RE, et al. Surveillance and follow-up strategies in patients with high-grade dysplasia in Barrett's esophagus: a dutch population-based study. *Am J Gastroenterol* 2012;107:534-542.  
 Wang KK, Sampliner RE. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. *Am J Gastroenterol* 2008;103:788-797.  
 Wilcox CM, Karowe MW. Esophageal infections: etiology, diagnosis, and management. *Gastroenterol* 1994;2:188-206.

### Stomach and Duodenum

American Gastroenterological Association position statement: evaluation of dyspepsia. *Gastroenterol* 1998;114:579-581.  
 Howden CW, Hunt RH. Guidelines for the management of helicobacter pylori infection. *Am J Gastroenterol* 1998;93:2330-2338.  
 Hunt RH, Fallone CA, Thomson ABR. Canadian helicobacter pylori consensus conference update: infection in adults. *J Gastroenterol* 1999;13:213-216.  
 Laine L, Peterson WL. Bleeding peptic ulcer. *NEJM* 1994;331:717-727.  
 Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcer. *Am J Gastroenterol* 1998;93:2037-2046.  
 McColl KE. Clinical practice helicobacter pylori infection. *NEJM*. 2010;362:1597-601.  
 Peek RM, Blaser MJ. Pathophysiology of helicobacter pylori-induced gastritis and peptic ulcer disease. *Am J Med* 1997;102:200-207.  
 Salcedo JA and Al-Kawas F. Treatment of helicobacter pylori infection. *Arch Intern Med* 1998;158:842-851.  
 Schmid CH, et al. Omeprazole plus antibiotics in the eradication of helicobacter pylori infection: a meta-regression analysis of randomized controlled trials. *Am J Ther* 1999;6:25-36.  
 Soll AH. Practice parameters: committee of the American College of Gastroenterology: medical treatment of peptic ulcer disease. *JAMA* 1996;275:622-629.  
 Thijs JC, et al. Diagnostic tests for helicobacter pylori: a prospective evaluation of their accuracy, without selecting a single test as the gold standard. *Am J Gastroenterol* 1996; 91:2125-2129.

### Small and Large Bowel

Aranda-Michel J and Giannella R. Acute diarrhea: a practical review. *Am J Med* 1999;670-676.  
 Colorectal cancer screening: recommendation statement from the canadian task force on preventative health care. *CMAJ* 2001;165:206-208.  
 Donowitz M, Kokke FT, Saidi R. Evaluation of patients with chronic diarrhea. *NEJM* 1995;332:725-729.  
 Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterol* 2006;130:1377-1390.  
 Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. *Lancet* 1974;2:394-397.  
 Ghosh S and Shand A. Ulcerative colitis. *BMJ* 2000;320:1119-1123.  
 Hanauer SB. Drug therapy: inflammatory bowel disease. *NEJM* 1996;334:841-848.  
 Hatchette TF, Farina D. Infectious diarrhea: when to test and when to treat. *CMAJ* 2011;183:339-344.  
 Horwitz BJ, Fisher RS. Current concepts: the irritable bowel syndrome. *NEJM* 2001;344:1846-1850.  
 Jennings JSR, Howdle PD. Celiac disease. *Curr Opin Gastroen* 2001;17:118-126.  
 Laine L, Sahota A, Shah A. Does capsule endoscopy improve outcomes in obscure gastrointestinal bleeding? Randomized trial vs. dedicated small bowel radiography. *Gastroenterol* 2010;138:1673-1680.

**Liver and Biliary Tract**

- Angulo P. Primary biliary cirrhosis and primary sclerosing cholangitis. *Clin Liv Dis* 1999;3:529-570.
- Andreoli T, Carpenter C, Griggs R, Loscalzo J, editors. *Cecil Essentials of Medicine*. 5th ed. Philadelphia: WB Saunders Company. c 2001.
- Custis K. Common biliary tract disorders. *Clin Fam Pract* 2000;2:141-154.
- Diehl AM. Alcoholic liver disease. *Clin Liv Dis* 1998;2:103-118.
- Feldman M, Friedman LS and Sleisenger MH, editors. *Gastrointestinal and Liver Disease. Pathophysiology/Diagnosis/Management*. 7th ed. Vol. 2.
- Haubrich WS, Schaffner F, Berk, JE. *Bockus Gastroenterology*. 5th ed. Vol 4. Chapter 74. *Pregnancy-Related Hepatic and Gastrointestinal Disorders*. Philadelphia: WB Saunders Company. c1995. p.1448-1458.
- Malik AH. Acute and chronic viral hepatitis. *Clin Fam Pract* 2000;2:35-57.
- Reynolds T. Ascites. *Clin Liv Dis* 2000;4:151-168.
- Sandowski SA. Cirrhosis. *Clin Fam Pract* 2000;2:59-77.
- Saunders. Chapter 184: Pregnancy and the Gastrointestinal Tract. p.3446-3452.
- Sherman M. Chronic viral hepatitis and chronic liver disease. *The Canadian Journal of Diagnosis* 2001;18:81-90.
- Sternlieb I. Wilson's disease. *Clin Liv Dis* 2000;4:229-239.
- Williams JW and Simel DL. Does this patient have ascites? *JAMA* 1992;267:2645-2648.
- Yapp TR. Hemochromatosis. *Clin Liv Dis* 2000;4: 211-228.
- Yu AS and Hu KQ. Management of ascites. *Clin Liv Dis* 2001;5:541-568.

**Pancreas**

- Beckinham IJ, Borman PC. Acute Pancreatitis. *BMJ* 2001;322:595-8.
- Beckinham IJ, Borman PC. Chronic Pancreatitis. *BMJ* 2001;322:595-8.
- Steer ML. Chronic pancreatitis. *NEJM* 1995;332:1482-90.
- Sternby B et al. What is the best biochemical test to diagnose acute pancreatitis? A prospective clinical study. *Mayo Clin Proc* 1996;71:1138-1144.
- Whytcomb DC. Acute pancreatitis. *NEJM* 2006;354:2142-2150.

**Rational Clinical Examination**

- Grover SA, Barkun AN, and Sackett DL. Does this patient have splenomegaly? *JAMA* 1993;270:2218-2221.
- Kitchens JM. Does this patient have an alcohol problem? *JAMA* 1994;272:1782-1787.
- Naylor CD. Physical exam of the liver. *JAMA* 1994;271:1859-1865.
- Williams JW and Simel DL. Does this patient have ascites? How to divine fluid in the abdomen. *JAMA* 1992;267:2645-2648.

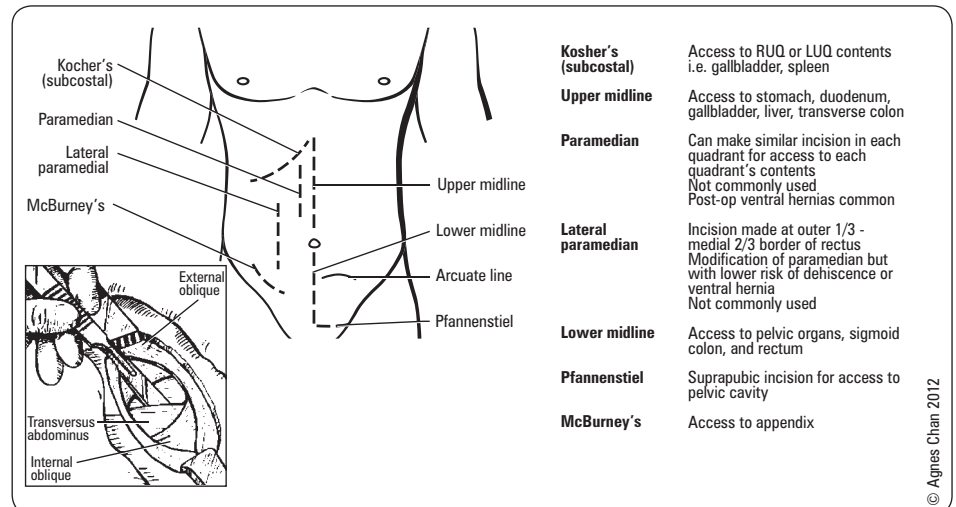
Nicolas Bowers and Nada Gawad, chapter editors  
 Jieun Kim and Daniel Soong, associate editors  
 Jeff Martin, EBM editor  
 Dr. Peter Stotland and Dr. Alice Wei, staff editors

<b>Acronyms</b> .....	<b>2</b>	<b>Diverticular Disease</b> .....	<b>31</b>
<b>Basic Anatomy Review</b> .....	<b>2</b>	Diverticulosis	
<b>Differential Diagnoses of Common Presentations</b> .....	<b>4</b>	Diverticulitis	
Acute Abdominal Pain		<b>Colorectal Neoplasms</b> .....	<b>33</b>
Abdominal Mass		Colorectal Polyps	
GI Bleeding		Familial Colon Cancer Syndromes	
Jaundice		Colorectal Carcinoma (CRC)	
<b>Preoperative Preparations</b> .....	<b>6</b>	<b>Other Conditions of the Large Intestine</b> . . .	<b>36</b>
<b>Surgical Complications</b> .....	<b>7</b>	Angiodysplasia	
Postoperative Fever		Volvulus	
Wound/Incisional Complications		Fistula	
Urinary and Renal Complications		Stomas	
Postoperative Dyspnea		<b>Anorectum</b> .....	<b>38</b>
Respiratory Complications		Hemorrhoids	
Cardiac Complications		Anal Fissures	
Intra-abdominal Abscess		Anorectal Abscess	
Paralytic Ileus		Fistula-In-Ano	
Delirium		Pilonidal Disease	
<b>Thoracic Surgery</b> .....	<b>12</b>	Rectal Prolapse	
Hiatus Hernia		Anal Neoplasms	
Esophageal Perforation		<b>Liver</b> .....	<b>41</b>
Esophageal Carcinoma		Liver Cysts	
Chest Wall		Liver Abscesses	
Pleura, Lung, and Mediastinum		Neoplasms	
Tube Thoracostomy		Liver Transplantation	
Lung Transplantation		<b>Biliary Tract</b> .....	<b>45</b>
Chronic Obstructive Pulmonary Disease		Cholelithiasis	
<b>Stomach and Duodenum</b> .....	<b>17</b>	Biliary Colic	
Peptic Ulcer Disease		Acute Cholecystitis	
Gastric Carcinoma		Acalculous Cholecystitis	
Gastrointestinal Stromal Tumour (GIST)		Choledocholithiasis	
Bariatric Surgery		Acute Cholangitis	
Complications of Gastric Surgery		Gallstone Ileus	
<b>Small Intestine</b> .....	<b>21</b>	Carcinoma of the Gallbladder	
Tumours of Small Intestine		Cholangiocarcinoma	
<b>Hernia</b> .....	<b>22</b>	<b>Pancreas</b> .....	<b>50</b>
Groin Hernias		Acute Pancreatitis	
<b>Bowel Obstruction</b> .....	<b>24</b>	Chronic Pancreatitis	
Small Bowel Obstruction (SBO)		Pancreatic Cancer	
Large Bowel Obstruction (LBO)		<b>Spleen</b> .....	<b>53</b>
<b>Colonic Pseudo-Obstruction</b> .....	<b>26</b>	Splenic Trauma	
Toxic Megacolon		Splenectomy	
Paralytic Ileus		<b>Breast</b> .....	<b>54</b>
Ogilvie's Syndrome		Benign Breast Lesions	
<b>Intestinal Ischemia</b> .....	<b>28</b>	Breast Cancer	
<b>Appendix</b> .....	<b>28</b>	<b>Surgical Endocrinology</b> .....	<b>59</b>
Appendicitis		Thyroid and Parathyroid	
Tumours of the Appendix		Adrenal Gland	
<b>Inflammatory Bowel Disease (IBD)</b> .....	<b>29</b>	Pancreas	
Crohn's Disease		<b>Pediatric Surgery</b> .....	<b>61</b>
Ulcerative Colitis		<b>Skin Lesions</b> .....	<b>64</b>
		<b>Common Medications</b> .....	<b>65</b>
		<b>References</b> .....	<b>65</b>

## Acronyms

AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ABI	ankle brachial index
APR	abdomino-perineal resection
BRBPR	bright red blood per rectum
CBD	common bile duct
CVA	costovertebral angle
CVP	central venous pressure
DIC	disseminated intravascular coagulation
DPL	diagnostic peritoneal lavage
EBL	estimated blood loss
OGD/EGD	esophagogastro-duodenoscopy
ERCP	endoscopic retrograde cholangiopancreatography
EUA	examination under anesthesia
EUS	endoscopic ultrasound
FAST	focused abdominal sonogram for trauma
FNA	fine needle aspiration
FOBT	fecal occult blood test
GERD	gastroesophageal reflux disease
HGCG	hereditary diffuse gastric carcinoma
HNPPC	hereditary nonpolyposis colorectal cancer
I&D	incision and drainage
LAR	low anterior resection
LBO	large bowel obstruction
LES	lower esophageal sphincter
LGIB	lower GI bleed
MAE	moving all extremities
MEN	multiple endocrine neoplasia
MIS	minimally invasive surgery
MRCP	magnetic resonance cholangiopancreatography
NGT	nasogastric tube
OGD	oesophagogastroduodenoscopy
POD	postoperative day
PTC	percutaneous transhepatic cholangiography
SBO	small bowel obstruction
SIADH	syndrome of inappropriate anti-diuretic hormone
TED	thrombo embolic deterrent
TEE	transesophageal echocardiogram
TTE	transthoracic echocardiogram
UGIB	upper GI bleed
VATS	video-assisted thorascopic surgery

## Basic Anatomy Review

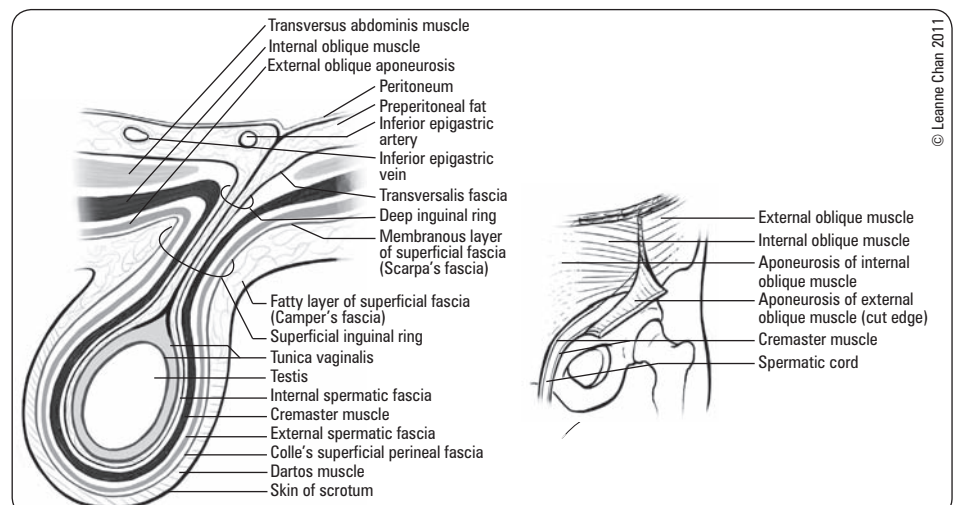


© Agnes Chan 2012

**Figure 1. Abdominal incisions**

### Layers from Superficial to Deep

- skin (epidermis, dermis, subcutaneous fat)
- superficial fascia
  - Camper's fascia (fatty) → Dartos
  - Scarpa's fascia (membranous) → Colles' superficial perineal fascia
- muscle (see Figure 2 and Figure 3)
  - external oblique → inguinal ligament → external spermatic fascia → fascia lata
  - internal oblique → cremasteric muscle/fascia
  - transversus abdominis → posterior inguinal wall
- transversalis fascia → internal spermatic fascia
- preperitoneal fat
- peritoneum → tunica vaginalis
- at midline
  - rectus abdominis muscle: in rectus sheath, divided by linea alba
- above arcuate line (semicircular line of Douglas), which is midway between symphysis pubis and umbilicus
  - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
  - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus muscle aponeurosis
- below arcuate line
  - anterior rectus sheath = aponeurosis of external, internal oblique, transversus muscles
  - posterior rectus sheath = transversalis fascia
- arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle



© Leanne Chan 2011

**Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord**



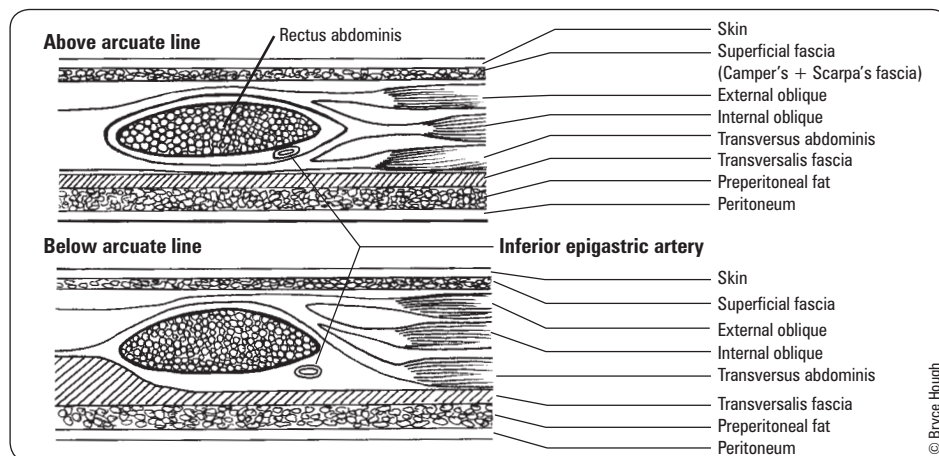


Figure 3. Midline cross-section of abdominal wall

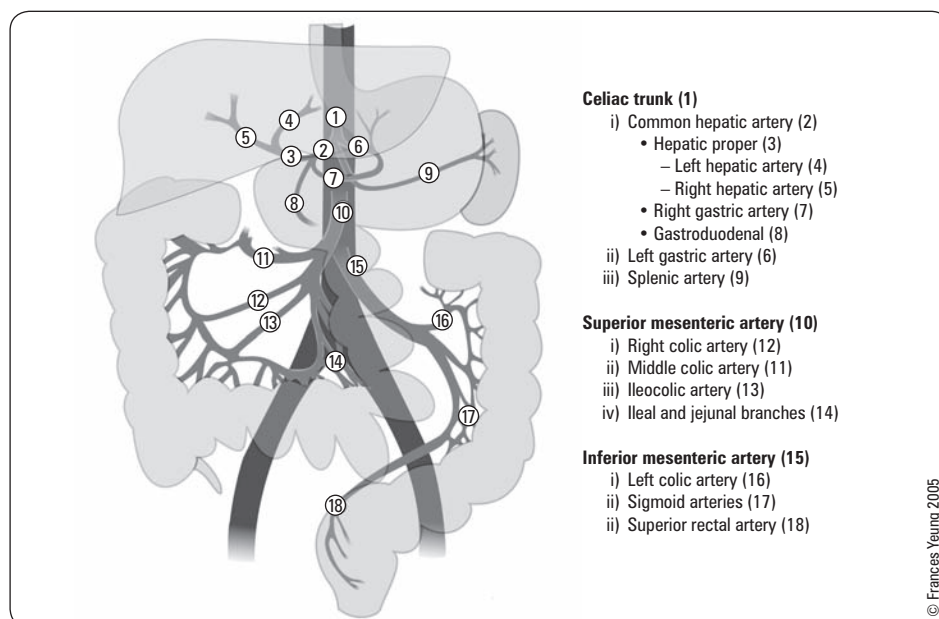


Figure 4. Blood supply to the GI tract

### Venous Flow

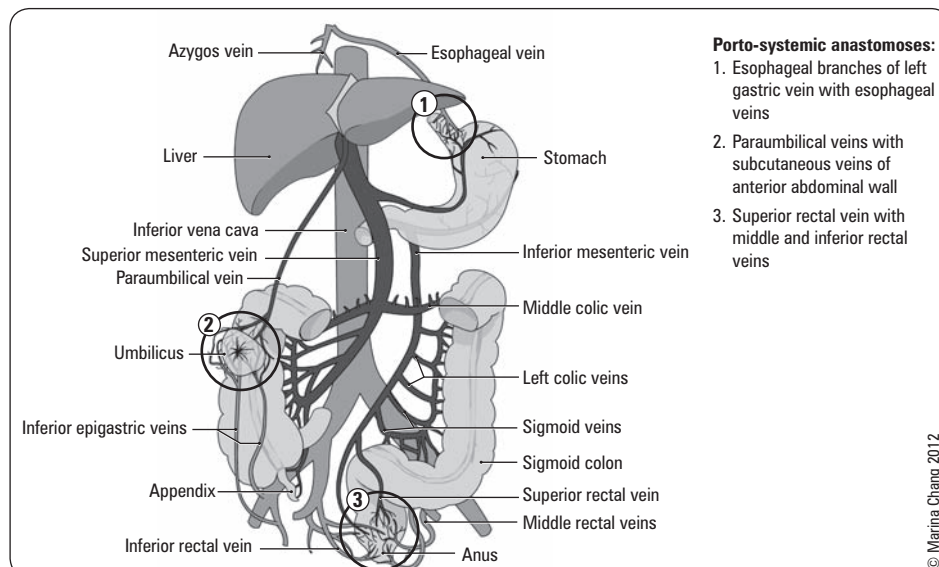


Figure 5. Venous drainage of the GI tract



Organ	Arteries
Liver	Left and right hepatic (branches of hepatic proper)
Spleen	Splenic
Gallbladder	Cystic (off right hepatic artery)
Stomach	1. Lesser curve: right and left gastric 2. Greater curve: right (off gastroduodenal) and left (off splenic) gastroepiploic (i.e. gastro-omental) 3. Fundus: short gastrics (off splenic)
Duodenum	1. Gastroduodenal 2. Pancreaticoduodenals (superior off gastroduodenal, inferior off superior mesenteric)
Pancreas	1. Splenic branches 2. Pancreaticoduodenals
Small intestine	1. Superior mesenteric branches: jejunal, ileal, ileocolic
Large intestine	1. Superior mesenteric branches: right colic, middle colic 2. Inferior mesenteric branches: left colic, sigmoid, rectal

# Differential Diagnoses of Common Presentations

## Acute Abdominal Pain

Table 1. Differential Diagnosis of Acute Abdominal Pain

RUQ	EPIGASTRIC	LUQ
<b>Hepatobiliary</b> Biliary colic Cholecystitis Cholangitis CBD obstruction (stone, tumour) Hepatitis Budd-Chiari Hepatic abscess/mass Right subphrenic abscess <b>Gastrointestinal</b> Pancreatitis Presentation of gastric, duodenal or pancreatic pathology Hepatic flexure pathology (CRC, subcostal incisional hernia) <b>Genitourinary</b> Nephrolithiasis Pyelonephritis Renal: mass, ischemia, trauma <b>Cardiopulmonary</b> RLL pneumonia Effusion/empyema CHF (causing hepatic congestion and R pleural effusion) MI Pericarditis Pleuritis <b>Miscellaneous</b> Herpes zoster Trauma Costochondritis	<b>Cardiac</b> Aortic dissection/ruptured AAA MI Pericarditis <b>Gastrointestinal</b> Gastritis GERD/esophagitis Peptic ulcer disease Pancreatitis Mallory-Weiss tear <b>DIFFUSE</b> <b>Gastrointestinal</b> Peritonitis Early appendicitis, perforated appendicitis Mesenteric ischemia Gastroenteritis/colitis Constipation Bowel obstruction Pancreatitis Inflammatory bowel disease Irritable bowel syndrome Ogilvie's syndrome <b>Cardiovascular/Hematological</b> Aortic dissection/ruptured AAA Sickle cell crisis <b>Genitourinary/Gynecological</b> Perforated ectopic pregnancy PID Acute urinary retention <b>Endocrinological</b> Carcinoid syndrome Diabetic ketoacidosis Addisonian crisis Hypercalcemia <b>Other</b> Lead poisoning Tertiary syphilis	<b>Pancreatic</b> Pancreatitis (acute vs. chronic) Pancreatic pseudocyst Pancreatic tumours <b>Gastrointestinal</b> Gastritis Peptic ulcer disease Splenic flexure pathology (e.g. CRC, ischemia) <b>Splenic</b> Splenic infarct/abscess Splenomegaly Splenic rupture Splenic aneurysm <b>Cardiopulmonary (see RUQ and Epigastric)</b> <b>Genitourinary (see RUQ)</b> <b>LLQ</b> <b>Gastrointestinal</b> Diverticulitis Diverticulosis Colon/sigmoid/rectal cancer Fecal impaction Proctitis (ulcerative colitis, infectious; i.e. gonococcus or chlamydia) Sigmoid volvulus Hernia <b>Gynecological</b> See 'suprapubic' <b>Genitourinary</b> See 'suprapubic' <b>Extraperitoneal</b> Abdominal wall hematoma/abscess Psoas abscess <b>See <a href="#">Gynecology</a>, <a href="#">Urology</a>, and <a href="#">Respirology</a> chapters for further details regarding respective RLQ and suprapubic pain</b>
RLQ	SUPRAPUBIC	
<b>Gastrointestinal</b> Appendicitis Crohn's disease Tuberculosis of the ileocecal junction Cecal tumour Intussusception Mesenteric lymphadenitis (Yersinia) Cecal diverticulitis Cecal volvulus Hernia: femoral, inguinal obstruction, Amyand's (and resulting cecal distention) <b>Gynecological</b> See 'suprapubic' <b>Genitourinary</b> See 'suprapubic' <b>Extraperitoneal</b> Abdominal wall hematoma/abscess Psoas abscess	<b>Gastrointestinal (see RLQ/LLQ)</b> Acute appendicitis IBD <b>Gynecological</b> Ectopic pregnancy PID Endometriosis Threatened/incomplete abortion Hydrosalpinx/salpingitis Ovarian torsion Hemorrhagic fibroid Tubo-ovarian abscess Gynecological tumours <b>Genitourinary</b> Cystitis (infectious, hemorrhagic) Hydrourter/urinary colic Epididymitis Testicular torsion Acute urinary retention <b>Extraperitoneal</b> Rectus sheath hematoma	



In all patients presenting with an acute abdomen, order the following:

### KEY TESTS FOR SPECIFIC DIAGNOSIS

- ALP, ALT, AST, bilirubin
- Amylase/lipase
- Urinalysis
- $\beta$ -hCG (in women of childbearing age)
- Troponins
- Lactate

### KEY TESTS FOR OR PREPARATION

- CBC, electrolytes, BUN, creatinine, glucose
- CXR + ECG
- INR/PTT



Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate laparotomy.



### Localization of Pain

Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation. Kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain.



### Referred Pain

- Biliary colic: to right shoulder or scapula
- Renal colic: to groin
- Appendicitis: periumbilical to right lower quadrant (RLQ)
- Pancreatitis: to back
- Ruptured aortic aneurysm: to back or flank
- Perforated ulcer: to RLQ (right paracolic gutter)
- Hip pain: to groin



### Most Common Presentations of Surgical Pain

- Sudden onset with rigid abdomen = perforated viscus
- Pain out of proportion to physical findings = ischemic bowel
- Vague pain that then localizes = appendicitis or other intra-abdominal process that irritates the parietal peritoneum
- Waves of colicky pain = bowel obstruction



### Types of Peritonitis

- Primary peritonitis: spontaneous without clear etiology
- Secondary peritonitis: due to a perforated viscus
- Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

## Abdominal Mass

**Table 2. Differential Diagnosis of Abdominal Mass**

Right Upper Quadrant (RUQ)	Upper Midline	Left Upper Quadrant (LUQ)
<b>Gallbladder:</b> cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis <b>Biliary tract:</b> Klatskin tumour <b>Liver:</b> hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)	<b>Pancreas:</b> pancreatic adenocarcinoma, other pancreatic neoplasm, pseudocyst <b>Abdominal aorta:</b> AAA (pulsatile) Gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma	<b>Spleen:</b> splenomegaly, tumour, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly <b>Stomach:</b> tumour
Right Lower Quadrant (RLQ)	Lower Midline	Left Lower Quadrant (LLQ)
<b>Intestine:</b> stool, tumour (CRC), mesenteric adenitis, appendicitis, appendiceal phlegmon or other abscess, typhlitis, intussusception, Crohn's inflammation <b>Ovary:</b> ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, Krukenberg) <b>Fallopian tube:</b> ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour	<b>Uterus:</b> pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra <b>GU:</b> bladder distention, tumour	<b>Intestine:</b> stool, tumour, abscess (see RLQ) <b>Ovary:</b> ectopic pregnancy, cyst, tumour (see RLQ) <b>Fallopian tube:</b> ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumour



### Indications for Urgent Operation

#### IHOP

Ischemia  
Hemorrhage  
Obstruction  
Perforation

## GI Bleeding

- see [Gastroenterology](#), G25

### Indications for Surgery

- failure of medical management
- hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage after initial stabilization procedures with up to two attempts of endoscopic hemostasis
- hypovolemic shock
- prolonged bleeding with transfusion requirement >3 units/d

### Surgical Management of GI Bleeding

- upper GI bleeding:
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia, hypotension, tachycardia)
  - initial management with endoscopy; if fails, then consider surgery
  - note: PUD accounts for approximately 55% of severe UGI bleeding
- lower GI bleeding:
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon
    - ♦ may occasionally present with melena
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - angiography, RBC scan to determine source as indicated
    - ♦ surgical intervention if no source found – obscure bleed

**Table 3. Differential Diagnosis of GI Bleeding**

Anatomical Source	Etiology	
<b>Hematological</b>	Excess anticoagulation (coumadin, heparin, etc.) Excess antiplatelet (clopidogrel, ASA)	Disseminated intravascular coagulation (DIC) Congenital bleeding disorders
<b>Nose</b>	Epistaxis	
<b>Esophagus</b>	Esophageal varices Mallory-Weiss tear Esophagitis	Aorto-esophageal fistula (generally post endovascular aortic repair)* Esophageal cancer
<b>Stomach</b>	Gastritis Gastric varices Dieulafoy's lesion	Gastric ulcer Gastric cancer*
<b>Duodenum</b>	Duodenal ulcer Perforated duodenal ulcer*	Duodenal cancer*
<b>Jejunum</b>	Tumours* Polyps Ulcers	



**Overt bleeding:** obvious hematochezia or melena per rectum visible to naked eye

**Occult bleeding:** bleeding per rectum is not obvious to naked eye (e.g. positive guaiac test)

**Obscure bleeding:** overt bleeding with no identifiable source after colonoscopy and endoscopy



### Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

NEJM 2013;368:11-21

Recent study by Villanueva et. al, demonstrates that a restrictive transfusion strategy significantly improves outcomes in patients with acute upper GI bleeding, compared to a liberal transfusion strategy. Refer to study for details.

**Table 3. Differential Diagnosis of GI Bleeding** (continued)

Anatomical Source	Etiology	
<b>Ileum and Ileocecal Junction</b>	Meckel's diverticulum (rare surgical management)	Crohn's disease*
	Small bowel obstruction	Tuberculosis of ileocecal junction
<b>Large Intestine</b>	Colorectal cancer*	Crohn's disease (less frequently presents with bleeding)*
	Mesenteric thrombosis/ischemic bowel*	Pancolitis (infectious, chemotherapy or radiation induced)
	Ulcerative colitis* (subtotal colectomy if failure of medical management)	Bleeding post-gastrointestinal anastomosis
	Angiodysplasia	
	Diverticula	
<b>Sigmoid</b>	Diverticulosis*	Polyps* (surgical management if not amenable to colonoscopic polypectomy)
	Sigmoid cancer*	Inflammatory bowel disease (IBD)
	Bleeding post-polypectomy	
<b>Rectum and Anus</b>	Hemorrhoids	Polyps* (surgical management if not amenable to polypectomy)
	Fissures	Crohn's or ulcerative colitis*
	Rectal cancer*	Solitary rectal ulcer syndrome
	Anal varices	

\*Managed surgically in most cases

## Jaundice

- see [Gastroenterology](#), G40

**Table 4. Differential Diagnosis of Jaundice**

<b>Pre-hepatic:</b> Pathology prior to the level of the liver Hemolysis Hyperthyroidism Portosystemic shunts Heart failure Large heme load (e.g. large hematoma reabsorption)	<b>Post-hepatic (obstructive):</b> Pathology after the conjugation of bilirubin in the liver
<b>Hepatic:</b> Pathology at the level of the liver Viral hepatitis Alcohol related hepatitis Non-alcohol related steatohepatitis Drug-induced hepatitis Dubin-Johnson syndrome Sepsis and hypoperfusion states TPN Infiltrative diseases (e.g. amyloidosis, lymphoma, sarcoidosis, tuberculosis) Hepatic crisis in sickle cell disease Pregnancy Cirrhosis End-stage liver disease	<b>Intraductal</b> Choledocholithiasis Sclerosing cholangitis Choledochal cyst Benign biliary stricture Cholangiocarcinoma AIDS cholangiopathy Autoimmune cholangiopathy Certain parasitic infections (e.g. <i>Ascaris lumbricoides</i> , liver flukes)  <b>Extraductal</b> Carcinoma: head of pancreas, ampulla of Vater, duodenum Lymphoma Metastases in peri-portal nodes Acute/chronic pancreatitis



### Biochemical Signs for Differentiating Jaundice

**Hepatocellular:** Elevated bilirubin + elevated ALT/AST  
**Cholestatic:** Elevated bilirubin + elevated ALP/GGT ± duct dilatation upon biliary U/S  
**Hemolysis:** ↓ haptoglobin ↑ LDH



**Note:** cholestatic jaundice is usually surgical.



### Bilirubin Levels

	Prehepatic	Intrahepatic	Posthepatic
<b>Serum bilirubin</b>			
Indirect	↑	↑	N
Direct	N	↑	↑
<b>Urine</b>			
Urobilinogen	↑	↑	–
Bilirubin	–	+	+
<b>Fecal</b>			
Urobilinogen	↑	↑	–



In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out.



### Best Practice in General Surgery (BPIGS)

<http://www.bpigs.ca/>  
 BPIGS is a University of Toronto initiative with the goal of standardizing care in general surgery. This link contains EBM based guidelines which have been implemented by consensus within all Toronto teaching hospitals. This is a highly recommended source for the most up to date pre-operative and general treatment guidelines.

## Preoperative Preparations

### Considerations

- informed consent (see [Ethical, Legal and Organizational Aspects of Medicine](#), ELOAM5)
- screening questionnaire to assess important potential risk factors such as age, exercise capacity, and medication use
- consults: anesthesia, medicine, cardiology as indicated
- NPO for ≥6 h prior, AAT (activity as tolerated), VSR (vital signs routine)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule → roughly 100-125 cc/h): normal saline or Ringer's lactate; bolus to catch up on estimated losses including losses from bowel prep
  - appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patient's regular medications including prednisone: consider pre-op stress dose if prednisone with β-blocker used in past year
- prophylactic antibiotics depending on wound class (within 1 h prior to incision): usually cefazolin (Ancef®) ± metronidazole (Flagyl®)
- bowel prep: cleans out bowel and decreases bacterial population
  - oral cathartic (e.g. fleet Phosphosoda®) starting previous day
  - in selected cases; current evidence does not support routine use
- consider DVT prophylaxis for all inpatient surgery (heparin)

- do not hold heparin prior to surgery unless epidural is expected
- hold ASA x 1 wk pre-op
- smoking cessation x 6 wk pre-op can significantly decrease post-op complications

### Investigations

- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, BUN, creatinine
- INR/PT, PTT
- ABGs if predisposed to respiratory insufficiency
- CXR (PA and lateral) if >50 yr old or previously abnormal within past 6 mo
- ECG if >50 yr old or as indicated by history
- $\beta$ -HCG testing in all women of reproductive age

### Drains

- nasogastric (NG) tube:
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding (only if necessary due to risk of aspiration → naso-jejunal tube preferable)
  - contraindications: suspected basal skull fracture, obstruction of nasal passages due to trauma
- Foley catheter with urometer:
  - indications: to accurately monitor urine output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  - contraindications: suspected urethral injury, difficult insertion of catheter



#### Approach to the Critically Ill Surgical/Trauma Patient

##### ABC, I'M FINE ABC

IV: 2 large bore IV's with NS, wide open  
Monitors: O<sub>2</sub> sat, ECG, BP  
Foley catheter to measure urine output  
Investigations: bloodwork  
NG tube if indicated  
"Ex" rays (abdomen 3 views, CXR),  
other imaging – only when stable



#### Pre and Post-Op Orders

##### ADDAVIDS

Admit to ward X under Dr. Y  
Diagnosis  
Diet  
Activity  
Vitals (q4h from ED and post-op is standard)  
IV, Investigations, Ins and Outs  
Drugs, Dressings, Drains  
Special procedures



#### Drugs – 6 As

Analgesia  
Anti-emetic  
Anti-coagulation  
Antibiotics  
Anxiolytics  
All other patient meds (home meds, stress dose steroids and  $\beta$ -blockers)



#### 5 Ws of Post-Op Fever

Wind POD #1-2 (pulmonary – atelectasis, pneumonia)  
Water POD #3-7 (urine – UTI)  
Wound POD #3-7  
Walk POD #8+ (thrombosis – DVT/PE)  
Wonder drugs POD #1+ (drug – fever)



#### Drain Size:

Measured by the unit French:  
French = diameter (mm) x 3

## Surgical Complications

### Postoperative Fever

- fever does not necessarily imply infection particularly in the first 24-48 h post-op
- fever may not be present or is blunted if patient is receiving chemotherapy, glucocorticoids or immunosuppression
- timing of fever may help identify cause
  - hours after surgery – POD #1 (immediate):
    - ♦ inflammatory reaction in response to trauma from surgery
    - ♦ reaction to blood products received during surgery
    - ♦ malignant hyperthermia
  - POD #1-2 (acute):
    - ♦ atelectasis (most common cause of fever on POD #1)
    - ♦ early wound infection (especially *Clostridium*, Group A *Streptococcus* – feel for crepitus and look for “dishwater” drainage)
    - ♦ aspiration pneumonitis
    - ♦ other: Addisonian crisis, thyroid storm, transfusion reaction
  - POD #3-7 (subacute): infections more likely
    - ♦ UTI, surgical site infection, IV site/line infection, septic thrombophlebitis, leakage at bowel anastomosis (tachycardia, hypotension, oliguria, abdominal pain)
  - POD #8+ (delayed):
    - ♦ intra-abdominal abscess, DVT/PE (can be anytime post-op, most commonly POD #8-10), drug fever
    - ♦ other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, *C. difficile* colitis, endocarditis

### Treatment

- treat primary cause
- antipyrexia (e.g. acetaminophen)

## Wound/Incisional Complications

### WOUND CARE

- can shower POD #2-3 after epithelialization of wound
- dressings can be removed POD #2 and left uncovered if dry
- examine wound if wet dressing, signs of infection (fever, tachycardia, pain)
- skin sutures and staples can be removed POD #7-10:
  - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, immunosuppressed) removed POD #14, earlier if signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin, ulcer)



## DRAINS

- sometimes placed intra-operatively to prevent fluid accumulation (blood, pus, serum, bile, urine)
  - can be used to assess quantity of third space fluid accumulation post-operatively
- potential route of infection, bring out through separate incision (vs. operative wound) to decrease risk of wound infection and remove as soon as possible
- types of drains
  - open (Penrose), higher risk of infection
  - closed (Jackson-Pratt, hemovac) connected to suction
  - pump (Daval) suction with airflow system to prevent obstruction
- monitor drain outputs daily
- drains should be removed once drainage is minimal (usually less than 30-50 cc/24 h)
- evidence does not support routine post-operative drainage of abdominal cavity

## SURGICAL SITE INFECTION

### Etiology

- *S. aureus*, *E. coli*, *Enterococcus*, *Streptococcus* spp., *Clostridium* spp.

### Risk Factors

- type of procedure:
  - clean (elective, not emergent, not traumatic, no acute inflammation, resp/GI/biliary/GU tracts not entered): <1.5%
  - clean-contaminated (elective entering of resp/GI/biliary/GU tracts): <3%
  - contaminated (nonpurulent inflammation, gross spillage from GI, entry into biliary or GU tracts with infected bile/urine, penetrating trauma <4 h old): 5%
  - dirty (purulent inflammation, pre-op perforation of resp/GI/biliary/GU tracts, penetrating trauma >4 h old): ~33-50%
  - increased risk with procedures >2 h long, use of drains
- patient characteristics:
  - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, chemotherapy
- other factors:
  - prolonged preoperative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts), skin preparation, hypoxemia, hypothermia

### Clinical Presentation

- typically fever POD #3-6 (*Streptococcus* and *Clostridium* can present in 24 h)
- pain, blanchable wound erythema, induration, frank pus or purulosanguinous discharge, warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, hernia

### Prophylaxis

- used to reduce the chance of surgical site infections
  - pre-op antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamycin):
    - within 1 h pre-incision; can re-dose at 1-2 half lives (~q4-8h) in the OR
    - not required for low risk elective cholecystectomy, hemorrhoidectomy, fistulotomy, sphincterotomy for fissure
- generally no need to continue prophylactic antibiotics postoperatively, reserve post-operative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C during OR)
- hyperoxygenation (consider FiO<sub>2</sub> of 80% in OR)
- chlorhexidine-alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving
- consider delayed primary closure of incision for contaminated wounds

### Treatment

- examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
- re-open affected part of incision, pack, heal by secondary intention
- antibiotics and demarcation of erythema only if cellulitis or immunodeficiency
- debride necrotic and non-viable tissue



#### Prophylactic Anastomotic Drainage for Colorectal Surgery

Cochrane DB Syst Rev 2004;2:CD002100

**Purpose:** To determine if prophylactic anastomotic drainage prevents complications after elective colorectal surgery.

**Methods:** Systematic review and meta-analysis of randomized-controlled trials (RCTs). Main outcome was clinical anastomotic dehiscence. Secondary outcomes were mortality, radiological anastomotic dehiscence, wound infection, reoperation, and extra abdominal complications.

**Results:** 6 RCTs (n = 1140 patients; n = 573 with drains, n = 567 no drains) were included. No statistically significant differences were found between drains and no drains in all outcomes.

**Conclusions:** Insufficient evidence to conclude if routine prophylactic anastomotic drainage prevents complications after colorectal surgery.



#### Systemic Prophylactic Antibiotics Recommendations

Updated Recommendations for Control of Surgical Site Infections

Ann Surg 2011;253:1082-93

- Choice of routine prophylactic antibiotic depends on the pathogen and patient allergies.
- Vancomycin and fluoroquinolones should be administered 1-2 h prior to incision. All other antibiotics should be administered 30 min prior to incision.
- Short-acting antibiotics should be redosed ~3 h after incision.
- Antibiotic administration >24 h after surgery does not appear to add benefits
- Antibiotics should no longer be routinely administered in three doses.
- The majority of antibiotics are renally excreted hence renal function must be considered in antibiotic administration
- Obese patients need higher antibiotic doses to achieve therapeutic concentrations
- Drug half-life and length of operation need to be considered in antibiotic administration



#### Examples of Wound Classification

**Clean:** elective inguinal herniorrhaphy

**Clean-contaminated:** cholecystectomy

**Contaminated:** necrotic bowel resection

**Dirty:** intra-abdominal abscess drainage



## WOUND HEMORRHAGE/HEMATOMA

- secondary to inadequate surgical control of hemostasis

### Risk Factors

- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial hypertension, severe cough
- more common with transverse incisions through muscle

### Clinical Features

- pain, swelling, discolouration of wound edges, leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency

### Treatment

- pressure dressing
- open drainage ± wound packing (large hematoma only)
- if significant bleeding, may need to re-operate to find source (often do not find a discrete vessel)

## SEROMA

- fluid collection other than pus or blood
- secondary to transection of lymph vessels
- delays healing
- increased infection risk

### Treatment

- pressure dressing ± needle drainage
- if significant may need to re-operate

## WOUND DEHISCENCE

- disruption of fascial layer, abdominal contents contained by skin only
- 95% caused by intact suture tearing through fascia

### Clinical Features

- typically POD #1-3, most common presentation sign is serosanguinous drainage from wound, ± evisceration (disruption of all abdominal layers and extrusion of abdominal contents – mortality of 15%)
- palpation of wound edge: should normally feel a “healing ridge” from abdominal wall closure (raised area of tissue under incision)

### Risk Factors

- local: technical failure of closure, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, patient not fully paralyzed while closing
- systemic: smoking, malnutrition (hypoalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, other (e.g. age, sepsis, uremia)
- diabetes mellitus alone is not a risk factor

### Treatment

- place moist dressing over wound with binder around abdomen and transfer to OR
- may consider conservative management with debridement of fascial and/or skin margins
- evisceration is a surgical emergency: take patient for operative closure, use slowly absorbable suture ± retention sutures



#### Preoperative Skin Antiseptics for Preventing Surgical Wound Infections after Clean Surgery *Cochrane DB Syst Rev 2013;3:CD003949*

**Purpose:** To determine if preoperative skin antiseptics prior to clean surgery prevents surgical-site infection (SSI) and which antiseptic is most effective.

**Methods:** Systematic review and meta-analysis of randomized-controlled trials (RCTs). Main outcome was SSI. Secondary outcomes included quality of life, mortality, and length of hospital stay.

**Results:** 13 RCTs (n = 2,623 patients) were included that made 11 total comparisons between skin antiseptics. A single study found a statistically significant difference between two antiseptics: 0.5% chlorhexidine solution in methylated spirits prevented SSIs after clean surgery better than alcohol-based povidone-iodine paint. No other statistically significant differences were found.

**Conclusions:** Insufficient evidence that one antiseptic is better than another. Alcohol-based solutions are probably more effective than aqueous-based solutions.



#### Prospective Randomized Trial of Two Wound Management Strategies for Dirty Abdominal Wounds *Ann Surg 2001;233:409-413*

**Purpose:** To determine the optimal method of wound closure for dirty abdominal wounds.

**Methods:** Patients (n = 51) with dirty abdominal wounds related to perforated appendicitis, other perforated viscus, traumatic injuries >4 h old, or intraabdominal abscesses were included. Patients were randomized to one of two wound management strategies: wound packed with saline-soaked gauze, evaluated 3 d after surgery for closure the next day if appropriate or primary closure. Wounds were considered infected if purulence discharged from the wound, or possibly infected if there were signs of inflammation or serous discharge.

**Results:** The wound infection rate was higher in the primary closure group than in the delayed packed closure group. Lengths of hospital stay and hospital charges were similar between the two groups.

**Conclusion:** Delayed packed closure is appropriate for dirty abdominal wounds with closure on day 4. This resulted in fewer wound infections and no increased duration of admission.

## Urinary and Renal Complications

### URINARY RETENTION

- may occur after any operation with general anesthesia or spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia, patients on anticholinergics

### Clinical Presentation

- abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL

### Treatment

- Foley catheter to rest bladder, then trial of voiding

**OLIGURIA/ANURIA** (see [Nephrology](#), NP33)**Etiology**

- pre-renal vs. renal vs. post-renal:
  - most common post-op cause is pre-renal  $\pm$  ischemic ATN
    - ♦ external fluid loss: hemorrhage, dehydration, diarrhea
    - ♦ internal fluid loss: third-spacing due to bowel obstruction, pancreatitis

**Clinical Presentation**

- urine output  $<0.5$  cc/kg/h, increasing Cr, increasing BUN

**Treatment**

- according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

## Postoperative Dyspnea

- see *Respiratory Complications* below and *Cardiac Complications*, GS11

**Etiology**

- respiratory: atelectasis, pneumonia, pulmonary embolus (PE), acute respiratory distress syndrome (ARDS), asthma, pleural effusion
- cardiac: MI, arrhythmia, CHF
- inadequate pain control

## Respiratory Complications

**ATELECTASIS**

- comprises 90% of post-op pulmonary complications

**Clinical Features**

- low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, tachypnea

**Risk Factors**

- COPD, smoking, obesity, elderly persons
- upper abdominal/thoracic surgery, oversedation, significant post-op pain, poor inspiratory effort

**Treatment**

- pre-operative prophylaxis
  - smoking cessation (best if  $>8$  wk pre-op)
- postoperative prophylaxis
  - incentive spirometry, deep breathing exercise, chest physiotherapy, intermittent positive-pressure breathing
  - selective nasogastric tube decompression after abdominal surgery
  - short-acting neuromuscular blocking agents
  - minimize use of respiratory depressive drug, good pain control, early ambulation

**PNEUMONIA/PNEUMONITIS**

- may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

**Risk Factors**

- aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NG tube, pregnancy, seizure disorder
- non-aspiration: atelectasis, immobility, pre-existing respiratory disease

**Clinical Features**

- productive cough, fever
- tachycardia, cyanosis, respiratory failure, decreased LOC
- CXR: pulmonary infiltrate

**Treatment**

- prophylaxis: see atelectasis prophylaxis, pre-op NPO/NG tube, rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. ceftriaxone, metronidazole)

**PULMONARY EMBOLUS** (see [Respirology](#), R17)**Clinical Features**

- unilateral leg swelling and pain (DVT as a source of PE), sudden onset SOB, tachycardia, fever
- most commonly POD #8-10, but can occur anytime post-op

**Treatment**

- IV heparin, long term warfarin (INR = 2-3) for 3 mo
- Greenfield (IVC) filter if contraindications to anticoagulation
- prophylaxis: subcutaneous heparin (5000 units bid) or LMWH, compression stockings (T.E.D. Hose)

**PULMONARY EDEMA****Etiology**

- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anaesthesia



New onset "asthma" and wheezing in the elderly is cardiogenic until proven otherwise.

**Clinical Features**

- shortness of breath, crackles at lung bases, CXR abnormal

**Treatment (LMNOP)**

- Lasix
- Morphine (decreases symptoms of dyspnea, venodilator and afterload reduction)
- Nitrates (venodilator)
- Oxygen + non-invasive ventilation
- Position (sit patient up)

**RESPIRATORY FAILURE****Clinical Features**

- dyspnea, cyanosis, evidence of obstructive lung disease
- earliest manifestations – tachypnea and hypoxemia (RR >25, pO<sub>2</sub> <60)
- pulmonary edema, unexplained decrease in SaO<sub>2</sub>

**Treatment**

- ABCs, O<sub>2</sub>, ± intubation
- bronchodilators, diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO<sub>2</sub> >60, consider acute respiratory distress syndrome (ARDS)

## Cardiac Complications

- abnormal ECGs common in post-op period (compare to pre-op ECG)
- common arrhythmias: supraventricular tachycardia (SVT), atrial fibrillation (secondary to fluid overload, PE, MI)

**MYOCARDIAL INFARCTION (MI)**

- see [Cardiology and Cardiovascular Surgery](#), C24
- surgery increases risk of MI
- incidence:
  - 0.5% in previously asymptomatic men >50 yr old
  - 40-fold increase in men >50 yr old with previous MI

**Risk Factors**

- pre-op hypertension, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intra-operative hypotension
- operations >3 h
- angina

**Clinical Features**

- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, hypotension

## Intra-abdominal Abscess

### Definition

- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

### Etiology

- usually polymicrobial: Gram-negative bacteria, anaerobes
  - consider Gram-positives if coexisting cellulitis

### Risk Factors

- emergency, contaminated OR
- GI surgery with anastomoses
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid re-distribution occurs

### Clinical Features

- persistent spiking fever, dull pain, weight loss
- mass difficult to palpate
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised, elderly)
- co-existing effusion (pleural effusion with subphrenic abscess)
- common sites: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, psoas

### Investigations

- CBC, blood cultures x2
- CT  $\pm$  water-soluble contrast
- DRE (pelvic abscess)

### Treatment

- eradication (preferred), laparoscopy, open drainage
- subsequent antibiotic coverage, ciprofloxacin (Cipro®) + metronidazole (Flagyl®)

## Paralytic Ileus

- see *Bowel Obstruction*, GS24

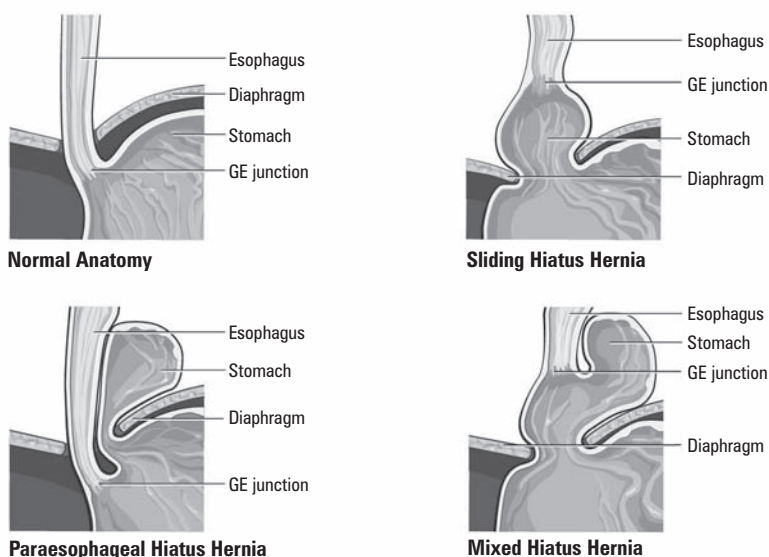
## Delirium

- see [Psychiatry](#), PS19 and [Neurology](#), N17



## Thoracic Surgery

### Hiatus Hernia



© Jenusha Ellis 2012

Figure 6. Types of hiatus hernia

**SLIDING HIATUS HERNIA (Type I)** (see Figure 6)

- herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

**Risk Factors**

- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, heavy lifting)
- smoking

**Clinical Features**

- majority are asymptomatic
- larger hernias frequently associated with GERD due to decreased competence of GE junction

**Complications**

- most common complication is GERD
- other complications are rare and are related to reflux:
  - esophagitis (dysphagia, heartburn)
  - consequences of esophagitis (peptic stricture, Barrett's esophagus, esophageal carcinoma)
  - extra-esophageal complications (pneumonitis/pneumonia, asthma, cough, laryngitis)

**Investigations**

- CXR, barium swallow, endoscopy, or esophageal manometry (technique for measuring LES pressure)
- 24-h esophageal pH monitoring to quantify reflux
- gastroscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett's esophagus and cancer

**Treatment**

- lifestyle modification:
  - stop smoking, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint and fat
- medical:
  - antacid, H<sub>2</sub>-antagonist, proton pump inhibitor, prokinetic agent
- surgical (<15%):
  - if failure of medical therapy, esophageal stricture, severe nocturnal aspiration, Barrett's esophagus
  - anti-reflux procedure (usually laparoscopic) e.g. Nissen fundoplication
    - ♦ fundus of stomach is wrapped around the lower esophagus and sutured in place
    - ♦ 90% success rate

**PARAESOPHAGEAL HIATUS HERNIA (Type II)** (see Figure 6)

- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
- least common esophageal hernia (<10%)

**Clinical Features**

- usually asymptomatic due to normal GE junction
- pressure sensation in lower chest, dysphagia

**Complications**

- hemorrhage, incarceration, strangulation, obstruction, gastric stasis ulcer

**Treatment**

- surgery to prevent severe complications:
  - reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
  - may consider suturing stomach to anterior abdominal wall (gastropexy)
  - in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy)

**MIXED HIATUS HERNIA (Type III)**

- combination of Types I and II

**TYPE IV HERNIA**

- herniation of other abdominal organs into thorax: colon, spleen, small bowel

**Differential Diagnosis of Hiatus Hernia**

GI Causes	Non-GI Causes
<ul style="list-style-type: none"> <li>• Cholelithiasis</li> <li>• Diverticulitis</li> <li>• Peptic ulcer</li> <li>• Achalasia</li> <li>• Pancreatitis</li> <li>• GERD</li> <li>• Gastritis</li> </ul>	<ul style="list-style-type: none"> <li>• MI</li> <li>• Angina</li> <li>• Pericarditis</li> </ul>

## Esophageal Perforation

### Etiology

- iatrogenic (most common):
  - endoscopic, dilatation, biopsy, intubation, operative, NG tube placement
- barogenic:
  - trauma
  - repeated, forceful vomiting (Boerhaave's syndrome)
  - other: convulsions, defecation, labour (rare)
- ingestion injury:
  - foreign body, corrosive substance
- carcinoma

### Clinical Features

- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, respiratory compromise
- subcutaneous emphysema, pneumothorax, hematemesis

### Investigations

- CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air
- CT chest: widened mediastinum, pneumomediastinum
- contrast swallow (water-soluble then thin barium): contrast extravasation

### Treatment

- supportive if rupture is contained:
  - NPO, vigorous fluid resuscitation, broad-spectrum antibiotics, possible percutaneous drainage
- surgical:
  - <24 h
    - ♦ primary closure of a healthy esophagus or resection of diseased esophagus
  - >24 h or non-viable wound edges
    - ♦ diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, gastrostomy/jejunostomy for decompression/feeding)

### Complications

- sepsis, abscess, fistula, empyema, mediastinitis, death
- post-op esophageal leak
- mortality 10-50% dependent on timing of diagnosis



**Boerhaave's syndrome:** transmural esophageal perforation

**Mallory-Weiss tear:** non-transmural esophageal tear (partial thickness tear)

Both are associated with forceful emesis.

## Esophageal Carcinoma

### Epidemiology

- M:F = 3:1
- onset 50-60 yr of age
- upper (20-33%), middle (33%), lower (33-50%)
- main types:
  - most common worldwide: squamous cell carcinoma (SCC) in upper 2/3 of esophagus
  - most common in western countries: adenocarcinoma in distal 1/3 of esophagus

### Risk Factors

- geographic variation in incidence
- SCC:
  - underlying esophageal disease such as strictures, diverticula, achalasia
  - more common in patients from Asia
- adenocarcinoma:
  - Barrett's esophagus (most important), smoking, obesity (increased reflux), GERD

### Clinical Features

- frequently asymptomatic: late presentation
- progressive dysphagia (mechanical): first solids then liquids
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis, anemia
- tracheoesophageal or bronchoesophageal fistula
- direct, hematogenous or lymphatic spread:
  - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac and mediastinal nodes



#### 4Ss of SCC

Smoking  
Spirits (alcohol)  
Seeds (betel nut)  
Scalding (hot liquid)



### Investigations

- barium swallow: shows narrowing – suggestive but not diagnostic
- esophagoscopy: biopsy and assess resectability
- endoscopic ultrasound (EUS):
  - visualize local disease
  - regional nodal involvement (most accurate way to stage the cancer)
- bronchoscopy ± thoracoscopy:
  - rule out airway invasion in tumours of the upper and mid esophagus
- CT chest/abdomen
- full metastatic workup (CXR, bone scan, CT-head/CAP, LTFs, etc.)

### Treatment

- if present with distant metastatic disease
  - treat with systemic therapy and treat symptoms (esophageal stent)
- if locally advanced (locally invasive disease or nodal disease on CT or EUS):
  - multimodal therapy:
    - ♦ concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
    - ♦ possibility of curative esophagectomy after chemoradiation if disease responds well
  - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if early stage (non-transmural and without evidence of nodal disease):
  - esophagectomy (trans thoracic or trans-hiatal approach) and lymphadenectomy
    - ♦ anastomosis in chest or neck
    - ♦ stomach most often used for reconstruction; may also use colon
  - neoadjuvant chemotherapy and radiation are controversial
  - adjuvant chemotherapy ± radiation usually recommended for post-op node-positive disease

### Prognosis

- prognosis usually poor because presentation is usually at advanced stage

### OTHER DISORDERS

- esophageal varices (see [Gastroenterology](#), G26)
- Mallory-Weiss tear (see [Gastroenterology](#), G27)



## Chest Wall

### CONGENITAL ABNORMALITIES

- pectus excavatum, pectus carinatum, sternal fissures
- surgery for cosmesis, psychosocial factors, respiratory or cardiovascular insufficiency (uncommon)

### THORACIC OUTLET SYNDROME

- impingement of subclavian vessels and brachial plexus nerve trunk

### Etiology

- congenital: cervical rib
- trauma
- degenerative: osteoporosis, arthritis

### Clinical Features

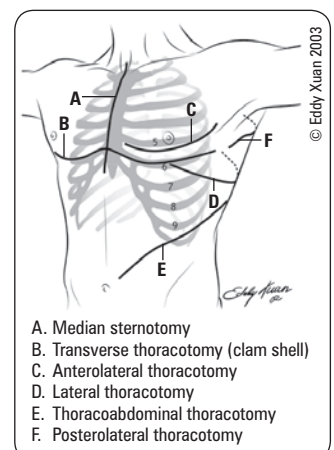
- neurogenic: ulnar and median nerve motor and sensory deficit
- arterial: fatigue, weakness, coldness, ischemic pain, paresthesia
- venous: edema, venous distention, collateral formation, cyanosis

### Treatment

- conservative (50-90%)
  - physiotherapy, posture and behaviour modification
- surgical: if conservative treatment fails, removal of first or cervical rib (if applicable)

### TUMOURS

- benign: fibrous dysplasia, eosinophilic granuloma, osteochondroma
- malignant: fibrosarcoma, chondrosarcoma, osteogenic sarcoma, Ewing's sarcoma, myeloma



**Figure 7. Typical thoracic surgery incisions**

## Pleura, Lung, and Mediastinum

- see [Respirology](#), R20



### Tube Thoracostomy

#### Indications

- to drain abnormal large-volume air or fluid collections in the pleural space
  - hemothorax, chylothorax, empyema
  - pneumothorax, if:
    - ♦ large or progressive
    - ♦ patient is on mechanical ventilation
    - ♦ bronchopleural fistula
    - ♦ tension pneumothorax
- to facilitate pleurodesis:
  - i.e. obliteration of the pleural space by instilling talc or doxycycline to cause fibrosis and adherence of parietal and visceral pleura
  - indicated for recurrent pleural effusions (often malignant)
- for long-term drainage of malignant effusions

#### Complications

- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators:
  - tubes may dissect along the external chest wall, or may be placed below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma
- risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0-1.5 L)

## Lung Transplantation

#### Conditions Leading to Transplantation

- chronic obstructive pulmonary disease (COPD), emphysema due to  $\alpha$ -1 antitrypsin deficiency
- cystic fibrosis (CF)
- idiopathic interstitial pneumonias: idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonitis
- idiopathic pulmonary arterial hypertension (IPAH), secondary pulmonary hypertension
- Eisenmenger's syndrome
- sarcoidosis, lymphangioleiomyomatosis, pulmonary Langerhan's cell histiocytosis

#### Clinical Indications

- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and limited expected survival over the next 2 yr

#### Criteria for Transplantation

- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

#### Contraindications

- uncontrolled or untreatable pulmonary or extrapulmonary infection
- malignancy in the last 2 yr
- advanced cardiopulmonary disease
- significant chest wall/spinal deformity
- active cigarette smoking
- HIV infection, ongoing HBV or HCV infections

#### Post-op Complications

- primary graft dysfunction: main cause is ischemia-reperfusion injury, graded by  $\text{PaO}_2/\text{FiO}_2$  ratio and CXR findings
- airway anastomotic complications (focal infection, bronchial necrosis and dehiscence, excess granulation tissue, tracheobronchomalacia, stenosis, fistula)
- chronic graft dysfunction: bronchiolitis obliterans syndrome

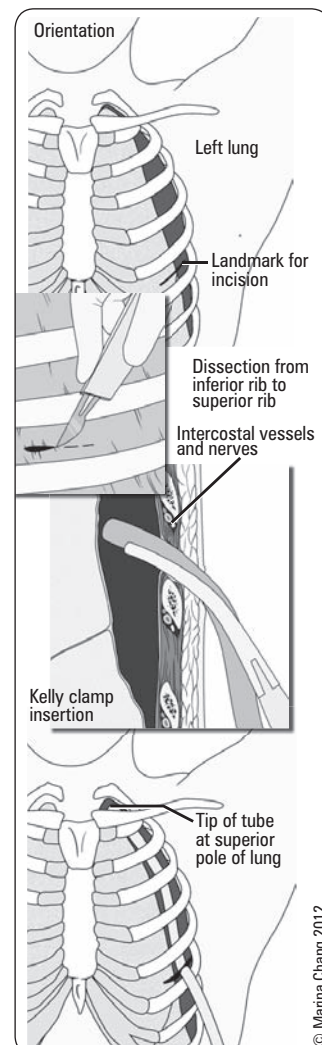


Figure 8. Tube thoracostomy

- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disease, colon, breast, Kaposi's sarcoma, bladder)

### Prognosis

- median survival for all adult recipients: 5.4 yr
- 1 yr survival: COPD > IPF > IPAHA
- 10 yr survival: CF,  $\alpha$ -1 antitrypsin deficiency > IPAHA > COPD, IPF

## Chronic Obstructive Pulmonary Disease

- see [Respirology](#), R8

### Treatment

- indications for surgical management:
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation
- contraindications:
  - age >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - $DL_{CO}$  <20% of predicted,  $PaCO_2$  >60 mm Hg,  $PaO_2$  <45 mmHg
- surgical procedures:
  - lung volume reduction surgery (LVRS): wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS

### Complications of Treatment

- air leak: may require reintubation and mechanical ventilation
- arrhythmias, pneumonia

### Prognosis

- total mortality at 2 yr same as with maximal medical therapy, but better exercise capacity and quality of life with LVRS



#### A Randomized Trial Comparing Lung Volume Reduction Surgery with Medical Therapy with Severe Emphysema

NEJM 2003;348:2059-2073

**Purpose:** To describe the outcomes of patients with severe emphysema who received pulmonary rehabilitation and lung-volume-reduction surgery or medical treatment.

**Methods:** Randomization of 1218 patients from 17 clinics to lung-volume-reduction surgery (bilateral stapled wedge resection by median sternotomy or video-assisted thoracic surgery) or continued medical treatment.

**Results:** More patients in the surgery group ( $n = 608$ ) had improved exercise capacity than the medical group ( $n = 610$ ) ( $p < 0.001$ ). After exclusion of patients at high mortality risk, no difference in overall mortality was found between the surgery and medical groups ( $p = 0.31$ ). For patients with predominantly upper-lobe emphysema and low exercise capacity ( $n = 290$ ), there was lower mortality in the surgery vs. medical group ( $p = 0.005$ ) and higher exercise capacity improvement in the surgery group ( $p < 0.001$ ). Mortality was higher in the surgery vs. medical group for patients with non-upper-lobe emphysema and high exercise capacity ( $n = 220$ ) ( $p = 0.02$ ).

**Conclusions:** No overall differences in mortality were found between the lung-volume-reduction surgery vs. medical groups. However, patients receiving surgery had improved exercise capacity. Patients with predominantly upper-lobe emphysema and low exercise capacity may be good candidates for lung-volume-reduction surgery while patients with non-upper-lobe emphysema and high exercise capacity may be poor candidates.



## Stomach and Duodenum



### Peptic Ulcer Disease

#### GASTRIC ULCERS

- see [Gastroenterology](#), G12

#### Indications for Surgery

- unresponsive to medical treatment (intractability):
  - always operate if fails to heal completely, even if biopsy negative: could be primary gastric lymphoma or adenocarcinoma
- dysplasia or carcinoma:
  - always biopsy ulcer for malignancy
- hemorrhage: 3x greater risk of bleeding compared to duodenal ulcers
- complications: obstruction, perforation, bleeding
- surgical treatment is increasingly rare due to *H. pylori* eradication and medical treatment

#### Procedures

- distal gastrectomy with ulcer excision: Billroth I or Billroth II (see Figure 9)
- vagotomy and pyloroplasty only if acid hypersecretion (rare)
- wedge resection if possible or biopsy with primary repair

#### DUODENAL ULCERS

- see [Gastroenterology](#), *Bleeding Peptic Ulcer*, G13 and *Peptic Ulcer Disease*, G12
- most within 2 cm of pylorus (duodenal bulb)

#### Indications for Surgery

- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
  - decision to operate based on amount of blood loss (usually >8 units), rate of bleeding and hemodynamic stability
- intractable despite medical management (endoscopy)



**Kissing ulcer:** combination of perforation and bleeding.



### Procedures

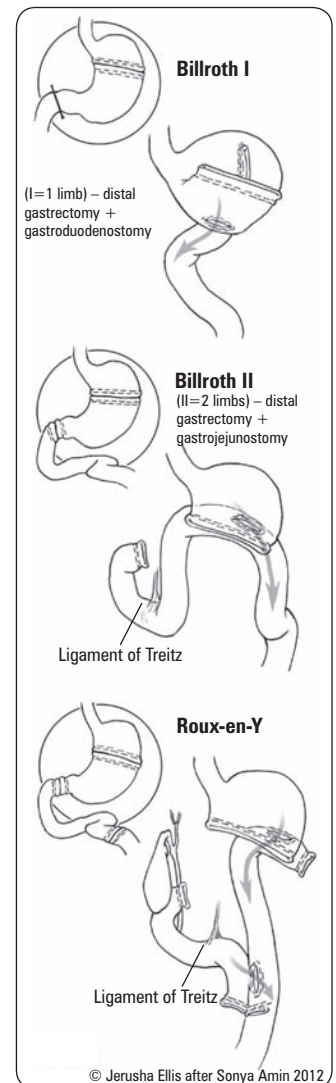
- Graham patch of perforated ulcer-plication of ulcer and omental patch
- oversewing of bleeding ulcer  $\pm$  pyloroplasty
- pyloroplasty, gastroduodenostomy or gastrojejunostomy (improved drainage)
- antrectomy (eliminate hormonal stimulation from the antrum)
- gastric resection (decrease the number of parietal cells)
- vagotomy
  - rarely done now due to *H. pylori* eradication and proton pump inhibitors

### Complications of Surgery

- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome (see *Complications of Gastric Surgery*, GS20)

**Table 5. Complications of Duodenal Ulceration**

Complication	Clinical Features	Management
<b>Perforated ulcer</b> (typically on anterior surface)	Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter) Acute abdomen: rigid, diffuse guarding Ileus Initial chemical peritonitis followed by bacterial peritonitis	Investigation: CXR – free air under diaphragm (70% of patients)  Treatment: Oversew ulcer (plication) and omental (Graham) patch – most common treatment
<b>Posterior penetration</b>	Elevated amylase/lipase if penetration into pancreas Constant mid-epigastric pain burrowing into back, unrelated to meals	
<b>Hemorrhage</b> (typically on posterior surface)	Gastroduodenal artery involvement	Resuscitation initially with crystalloids; blood transfusion if necessary Diagnostic and/or therapeutic endoscopy (laser, cautery or injection); if recurs, may have second scope Consider interventional radiology: angiography with embolization/coiling Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty
<b>Gastric outlet obstruction</b>	Ulcer can lead to edema, fibrosis of pyloric channel, neoplasm Nausea and vomiting (undigested food, non-bilious), dilated stomach, crampy abdominal pain Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken) Auscultate gas and fluid movement in obstructed organ	NG decompression and correction of hypochloremic, hypokalemic metabolic alkalosis Medical management initially: high dose PPI therapy Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty or gastrojejunostomy



**Figure 9. Billroth I and Billroth II with roux-en-y reconstruction (gastrojejunostomy)**

## Gastric Carcinoma

### Epidemiology

- male:female = 3:2
- incidence of adenocarcinoma <10 (U.S.) vs. 60 (Japan, Korea) per 100,000 (incidence highest in Asia and Latin America)
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr

### Risk Factors

- *H. pylori*, causing chronic atrophic gastritis
- hereditary nonpolyposis colorectal cancer (HNPCC), hereditary diffuse gastric carcinoma (HDGC)
- smoking, alcohol, smoked food, nitrosamines
- pernicious anemia associated with achlorhydria and chronic atrophic gastritis
- gastric adenomatous polyps
- previous partial gastrectomy (>10 yr post-gastrectomy)
- hypertrophic gastropathy
- blood type A

## Clinical Features

- clinical suspicion:
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious or late onset of symptoms:
  - postprandial abdominal fullness, vague epigastric pain
  - anorexia, weight loss
  - burping, nausea, vomiting, dyspepsia, dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, iron-deficiency anemia
- metastasis:
  - peritoneum, liver, lung, brain

## Investigations

- OGD and biopsy; EUS to assess preoperative T-stage and N-stage
- chest/abdo/pelvis CT (for metastatic work-up see Table 7)

**Table 6. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2010)**

Primary Tumour (T)		Regional Lymph Nodes (N)		Distant Metastasis (M)	
T0	No evidence of primary tumour	NX	Cannot be assessed	M0	No distant metastasis
Tis	Carcinoma in situ	N0	No regional node	M1	Distant metastasis
T1a	Invasion into lamina propria or muscularis mucosae	N1	Metastasis in 1-2 regional nodes		
T1b	Invasion into submucosa	N2	Metastasis in 3-6 regional nodes		
T2	Invasion into muscularis propria	N3a	Metastasis in 7-15 regional nodes		
T3	Penetration of subserosal connective tissue without tissue invasion of visceral peritoneum or adjacent structures	N3b	Metastasis in ≥16 regional nodes		
T4a	Invasion into serosa				
T4b	Invasion into adjacent structures				

## Treatment

- adenocarcinoma:
  - proximal lesions:
    - total gastrectomy and esophagojejunostomy – Roux-en-Y (see Figure 9)
  - distal lesions:
    - distal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes
  - palliation:
    - gastric resection to decrease bleeding and relieve obstruction, enables the patient to eat
    - radiation therapy
    - studies are showing larger role for chemotherapy
- lymphoma:
  - H. pylori* eradication, chemotherapy ± radiation, surgery in limited cases (perforation, bleeding, obstruction)



### Signs of Metastatic Gastric Carcinoma

**Virchow's node:** left supraclavicular node

**Blumer's shelf:** mass in pouch of Douglas

**Krukenberg tumour:** metastases to ovary

**Sister Mary Joseph node:** umbilical metastases

**Irish's node:** left axillary nodes



### Staging and 5-year Survival Rates for Gastric Cancer

Stage	TNM	5-Year Survival
IA	T1N0M0	71%
IB	T2N0M0 T1N1M0	57%
IIA	T3N0M0 T2N1M0 T1T2M0	45%
IIB	T4aN0M0 T3N1M0 T2N2M0 T1N3M0	33%
IIIA	T4aN1M0 T3T2M0 T2N3M0	20%
IIIB	T4bN0M0 T4bN1M0 T4aN2M0 T3N3M0	14%
IIIC	T4bN2M0 T4bN3M0 T4aN3M0	9%
IV	TxNxM1	4%



### Bariatric (Weight Loss) Surgery for Obesity is Considered when Other Treatments have Failed

#### Benefits

- Greater weight loss in patients with BMI >30 at 2 yr
- Reduction in co-morbidities (Type II diabetes, hypertension and medication use)
- Improvement in quality of life at 2 yr (physical function, physical role, general health, vitality and emotional role)

#### Risks

- Complications: leaks, hernias, infection, pulmonary embolism, postoperative mortality
- Side effects specific to type of procedure (i.e. vomiting, dumping syndrome, food intolerance)
- Cholecystitis occurs as a result of rapid weight loss

Cochrane DB Syst Rev 2009;2:CD003641

## Gastrointestinal Stromal Tumour (GIST)

### Epidemiology

- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- often discovered incidentally on CT, laparotomy or endoscopy

### Risk Factors

- Carney's triad: GISTs, paraganglioma, and pulmonary chondroma
- Type IA neurofibromatosis



### Investigations

- pre-operative biopsy: controversial, but useful for indeterminate lesions:
  - not recommended if index of suspicion for GIST is high
  - percutaneous biopsy is NOT recommended due to high friability and risk of peritoneal spread

### Treatment

- surgical resection if >2 cm; follow with serial endoscopy if <2 cm and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT recommended, as GISTs rarely metastasize to lymph nodes
  - consider imatinib postop for high-risk GIST (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - chemotherapy with imatinib

### Prognosis

- risk of metastatic potential depends on:
  - tumour size (worse if >10 cm)
  - mitotic activity (worse if >5 mitotic figures or 50/hpf)
  - degree of nuclear pleomorphism
  - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- metastases to liver, omentum, peritoneum; nodal metastases rare

## Bariatric Surgery

- weight reduction surgery for morbid obesity
- indications: BMI >40 or BMI >35 with related comorbidity (e.g. DM, CAD, sleep apnea, severe joint disease)
- requires multidisciplinary evaluation and follow-up

### Surgical Options

- malabsorptive/restrictive:
  - laparoscopic Roux-en-Y gastric bypass (most common – see Figure 9)
  - staple off small gastric pouch (restrictive) with Roux-en-Y limb to pouch (malabsorptive) with dumping syndrome physiology
  - most effective, higher complication rates
- restrictive:
  - laparoscopic adjustable gastric banding
    - silicone band around fundus creates pouch, adjustable through port under skin
  - laparoscopic vertical banded gastroplasty
    - vertical stapled small gastric pouch with placement of silastic ring band
- malabsorptive:
  - biliopancreatic diversion with duodenal switch
  - gastrectomy, enteroenterostomy, duodenal division closure and duodenoenterostomy

### Complications

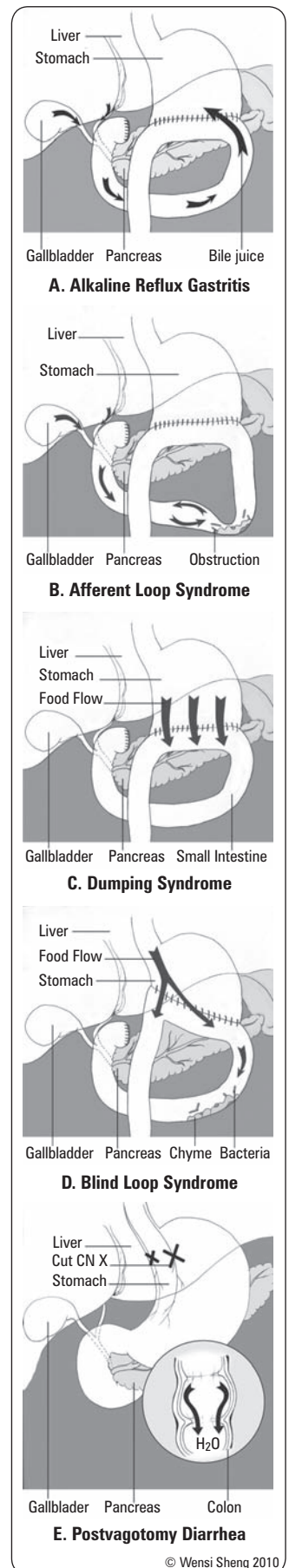
- perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
- obstruction at enteroenterostomy (see *Complications of Gastric Surgery*, below)
- staple line dehiscence
- dumping syndrome
- cholelithiasis due to rapid weight loss (20-30%)
- band abscess (if long-term)

## Complications of Gastric Surgery

- most resolve within 1 yr (see Figure 10)

### Alkaline Reflux Gastritis (see Figure 10A)

- duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
- treatment:
  - medical: H<sub>2</sub>-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  - surgical: conversion of Billroth I or II to Roux-en-Y



**Figure 10. Complications of gastric surgery**



**Afferent Loop Syndrome** (see Figure 10B)

- accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
- clinical features:
  - early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
- treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)



Keep/maintain a very low threshold for laparoscopy in patients with abdominal pain after gastric bypass.

**Dumping Syndrome** (see Figure 10C)

- early – 15 min post-prandial:
  - etiology:
    - ♦ hyperosmotic chyme released into small bowel (fluid accumulation and jejunal distention)
  - clinical features:
    - ♦ post-prandial symptoms
    - ♦ epigastric fullness or pain, emesis, nausea, diarrhea, palpitations, dizziness, tachycardia, diaphoresis
  - treatment:
    - ♦ small multiple low carbohydrate, low fat and high protein meals and avoidance of liquids with meals
    - ♦ last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
- late – 3 h post-prandial:
  - etiology: large glucose load leads to large insulin release and hypoglycemia
  - treatment: small snack 2 h after meals

**Blind-Loop Syndrome** (see Figure 10D)

- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features:
  - anemia/weakness, diarrhea, malnutrition, abdominal pain and hypocalcemia
- treatment: broad-spectrum antibiotics, surgery (conversion to Billroth I)

**Postvagotomy Diarrhea** (see Figure 10E)

- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine), surgical (reversed interposition jejunal segment)

## Small Intestine

### Tumours of Small Intestine

**BENIGN TUMOURS**

- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum, proximal jejunum
- polyps:
  - adenomas
  - hamartomas
  - familial adenomatous polyposis (FAP) (see *Familial Colon Cancer Syndromes*, GS33)
  - juvenile polyps
- other: leiomyomas, lipomas, hemangiomas

**Malignant Tumours – ACLS**

Adenocarcinoma      Most common  
 Carcinoid  
 Lymphoma  
 Sarcoma              Least common

↓

**Carcinoid Syndrome Symptoms – FDR**

Flushing  
 Diarrhea  
 Right-sided heart failure

**Table 7. Malignant Tumours of the Small Intestine**

	Adenocarcinoma	Carcinoid	Lymphoma	Metastatic
<b>Epidemiology</b>	Usually 50-70 yr old M>F	Increased incidence 50-60 yr old	Highest incidence in 70s M>F Usually non-Hodgkin's lymphoma	Most common site of GI metastases in patients with metastatic melanoma
<b>Risk Factors</b>	FAP, history of colorectal cancer (CRC), HNPCC		Crohn's, celiac disease, autoimmune disease, immunosuppression, radiation therapy, nodular lymphoid hyperplasia	Melanoma, breast, lung, ovary, colon, cervical cancer

Table 7. Malignant Tumours of the Small Intestine (continued)

	Adenocarcinoma	Carcinoid	Lymphoma	Metastatic
<b>Clinical Features</b>	Early metastasis to LNs 80% metastatic at time of operation Abdo pain (common)	Nausea, vomiting, anemia, GI bleeding, jaundice, weight loss (less common) Often slow-growing Usually asymptomatic, incidental finding Obstruction, bleeding, crampy abdominal pain, intussusception Carcinoid syndrome (<10%): • Hot flashes, hypotension, diarrhea, bronchoconstriction, right heart failure • Requires liver involvement: lesion secretes serotonin, kinins and vasoactive peptides directly to systemic circulation (normally inactivated by liver)	Fatigue, weight loss, fever malabsorption, abdo pain, anorexia, vomiting, constipation, mass Rarely – perforation, obstruction, bleeding, intussusception	Obstruction and bleeding
<b>Investigations</b>	CT abdo/pelvis Endoscopy	Most found incidentally at surgery for obstruction or appendectomy Chest thorax/abdo/pelvis Consider small bowel enteroclysis to look for primary Elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood Radiolabelled octreotide or MIBG scans to locate tumour	CT abdo/pelvis	CT abdo/pelvis
<b>Treatment</b>	Surgical resection ± chemotherapy	Surgical resection ± chemotherapy Carcinoid syndrome treated with steroids, histamine, octreotide Metastatic risk 2% if size <1 cm, 90% if >2 cm	Low grade: chemotherapy with cyclophosphamide High grade: surgical resection, radiation Palliative: somatostatin, doxorubicin	Palliation
<b>Prognosis</b>	5-yr survival 25% (if node positive)	5 yr survival 70%; 20% with liver metastases	5-yr survival 40%	Poor
<b>Origin/Location</b>	Usually in proximal small bowel, incidence decreases distally	Classified based on embryological origin (foregut, midgut, hindgut) Originate from gut enterochromaffin cell Appendix 46%, distal ileum 28%, rectum 17%	Usually distal ileum Proximal jejunum in patients with celiac disease	Hematogenous spread from breast, lung, kidney Direct extension from cervix, ovaries, colon
<b>Staging System</b>	TNM	TNM	Ann Arbor	

## Hernia

### Definition

- fascial defect → protrusion of a viscus into an area in which it is not normally contained

### Epidemiology

- M:F = 9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- 50% are indirect inguinal hernia, 25% are direct inguinal hernia, 5% are femoral
- most common surgical disease of males

### Risk Factors

- activities which increase intra-abdominal pressure:
  - obesity, chronic cough, pregnancy, constipation, straining on urination or defecation, ascites, heavy lifting
- congenital abnormality (e.g. patent processus vaginalis)
- previous hernia repair

### Clinical Features

- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

### Investigations

- physical examination usually sufficient
- ultrasound ± CT (CT required for obturator hernias, internal abdominal hernias and Spigelian femoral hernias in obese patients)

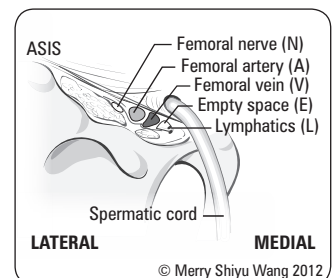


Figure 11. Normal inguinal anatomy



### Borders of Hesselbach's Triangle

- Lateral: inferior epigastric artery
- Inferior: inguinal ligament
- Medial: lateral margin of rectus sheath

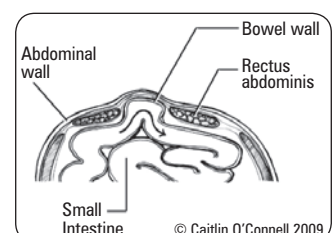


Figure 12. Richter's hernia

## Classification

- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  - requires **emergency** repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter's hernia: only part of bowel circumference (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
  - a strangulated Richter's hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation
- sliding hernia: part of wall of hernia formed by protruding viscus (usually cecum)

## Anatomical Types

- groin (see Tables 8 and 9)
  - indirect and direct inguinal, femoral (see Figure 13)
  - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre's (involving Meckel's), Amyand's (containing appendix), lumbar, obturator, parastomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

## Complications

- incarceration: irreducible
- strangulation: irreducible with resulting ischemia
  - small, new hernias more likely to strangulate
  - femoral >> indirect inguinal > direct inguinal
  - intense pain followed by tenderness
  - intestinal obstruction, gangrenous bowel, sepsis
  - surgical emergency
  - **DO NOT** attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous
    - ♦ will cause closed loop SBO – and EMERGENCY

## Treatment

- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, for cosmesis; if asymptomatic can delay surgery
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

## Postoperative Complications

- recurrence (15-20%):
  - risk factors: recurrent hernia, age >50, smoking, BMI >25, poor pre-op functional status (ASA ≥3 – see [Anesthesia](#), A3), associated medical conditions: type II DM, hyperlipidemia, immunosuppression, any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/"tension-free" repair
- scrotal hematoma (3%):
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
- nerve entrapment:
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein:
  - acute leg swelling
- ischemic colitis



### Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men: A Randomized Clinical Trial

JAMA 2006;295:285-292

**Purpose:** To compare pain and the physical component score (PCS) of the Short Form-36 Version 2 survey at 2 yr in men with minimally symptomatic inguinal hernias treated with watchful waiting or surgical repair.

**Methods:** RCT of 720 men (n=364 watchful waiting, n=356 surgical repair) followed up for 2-4.5 yr. Watchful-waiting patients were followed up at 6 mo and annually and watched for hernia symptoms; repair patients received standard open tension-free repair and were followed up at 3 and 6 mo and annually. The main outcome was pain and discomfort interfering with usual activities at 2 yr and change in PCS from baseline to 2 yr. Secondary outcomes were complications, patient-reported pain, functional status, activity levels, and satisfaction with care.

**Results:** Primary intention-to-treat outcomes were similar at 2 yr for watchful waiting vs. surgical repair: pain limiting activities (5.1% vs. 2.2%, respectively; P = .06 [corrected]); PCS (improvement over baseline, 0.29 points vs. 0.13 points; P = .79). Twenty-three percent of patients assigned to watchful waiting crossed over to receive surgical repair (increase in hernia-related pain was the most common reason offered); 17% assigned to receive repair crossed over to watchful waiting. Self-reported pain in watchful-waiting patients crossing over improved after repair. Occurrence of postoperative hernia-related complications was similar in patients who received repair as assigned and in watchful-waiting patients who crossed over. One watchful-waiting patient (0.3%) experienced acute hernia incarceration without strangulation within 2 yr; a second had acute incarceration with bowel obstruction at 4 yr, with a frequency of 1.8/1000 patient/yr inclusive of patients followed up for as long as 4.5 yr.

**Conclusion:** Watchful waiting is an acceptable option for men with minimally symptomatic inguinal hernias. Delaying surgical repair until symptoms increase is safe because acute hernia incarcerations occur rarely.



### Inguinal Hernias – MD's don't Lie

MD: Medial to the inferior epigastric a.  
= Direct inguinal hernia  
LI: Lateral to the inferior epigastric a.  
= Indirect inguinal hernia



**Inguinal canal walls = MALT x 2**  
(starting superior, moving around posterior)

Roof	<b>2M</b>	2 muscles
Ant. wall	<b>2A</b>	2 aponeuroses
Floor	<b>2L</b>	2 ligaments
Post. wall	<b>2T</b>	2 tendons



Cooper's Ligament, which runs on the pectineal line of the pubic bone, is often exploited in hernia repair.



### Contents of Spermatic Cord

vas deferens, testicular artery/veins, genital branch of genitofemoral nerve, lymphatics, cremaster muscle, ± hernia sac

## Groin Hernias

Table 8. Groin Hernias

	Direct Inguinal	Indirect Inguinal	Femoral
<b>Epidemiology</b>	1% of all men	Most common hernia in men and women Males > females	Affects mostly females
<b>Etiology</b>	Acquired weakness of transversalis fascia "Wear and tear" Increased intra-abdominal pressure	Congenital persistence of processus vaginalis in 20% of adults	Pregnancy – weakness of pelvic floor musculature Increased intra-abdominal pressure
<b>Anatomy</b>	Through Hesselbach's triangle <b>Medial</b> to inferior epigastric artery Usually does not descend into scrotal sac	Originates in deep inguinal ring <b>Lateral</b> to inferior epigastric artery Often descends into scrotal sac (or labia majora)	Into femoral canal, below inguinal ligament but may override it Medial to femoral vein within femoral canal
<b>Treatment</b>	Surgical repair	Surgical repair	Surgical repair
<b>Prognosis</b>	3-4% risk of recurrence	<1% risk of recurrence	

Table 9. Superficial Inguinal Ring vs. Deep Inguinal Ring

Superficial Inguinal Ring	Deep Inguinal Ring
Opening in external abdominal aponeurosis; palpable superior and lateral to pubic tubercle	Opening in transversalis fascia: palpable superior to mid-inguinal ligament
Medial border: medial crus of external abdominal aponeurosis	Medial border: inferior epigastric vessels
Lateral border: lateral crus of external oblique aponeurosis	Superior-lateral border: internal oblique and transversus abdominis muscles
Roof: intercrural fibres	Inferior border: inguinal ligament

## Bowel Obstruction



### Definition

- partial or complete blockage of the bowel resulting in failure of intestinal contents to pass through lumen

### Pathogenesis

- disruption of the normal flow of intestinal contents → proximal dilatation + distal decompression
- may take 12-24 h to decompress, therefore passage of feces and flatus may occur after the onset of obstruction
- bowel ischemia may occur if blood supply is strangulated or bowel wall inflammation leads to venous congestion
- bowel wall edema and disruption of normal bowel absorptive function → increased intraluminal fluid → transudative fluid loss into peritoneal cavity, electrolyte disturbances

### Differential Diagnosis

- small bowel obstruction (SBO), large bowel obstruction (LBO), pseudo-obstruction

### Clinical Features

- must differentiate between obstruction and ileus, and characterize obstruction as acute vs. chronic, partial vs. complete (constipation vs. obstipation), small vs. large bowel, strangulating vs. non-strangulating, and with vs. without perforation

Table 10. Bowel Obstruction vs. Paralytic Ileus

	SBO	LBO	Paralytic Ileus
<b>Nausea, Vomiting</b>	Early, may be bilious	Late, may be feculent	Present
<b>Abdominal Pain</b>	Colicky	Colicky	Minimal or absent
<b>Abdominal Distention</b>	+ (prox SBO), ++ (distal SBO)	++	+
<b>Constipation</b>	+	+	+
<b>Other</b>	± visible peristalsis	± visible peristalsis	
<b>Bowel Sounds</b>	Normal, increased Absent if secondary ileus	Normal, increased (borborygmi) Absent if secondary ileus	Decreased, absent
<b>AXR Findings</b>	Air-fluid levels "Ladder" pattern (plicae circularis) Proximal distention (>3 cm) + no colonic gas	Air-fluid levels "Picture frame" appearance Proximal distention + distal decompression No small bowel air if competent ileocecal valve Coffee bean sign	Air throughout small bowel and colon

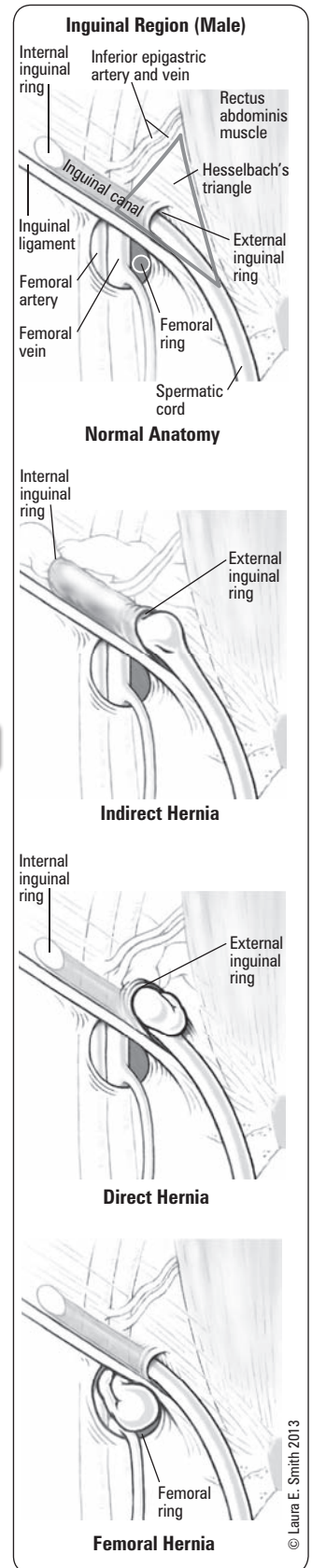


Figure 13. Schematic of inguinal (direct and indirect) and femoral hernias

### Complications (of total obstruction)

- strangulating obstruction (10% of bowel obstructions) = **surgical emergency**:
  - cramping pain turns to continuous ache, hematemesis, melena (if infarction)
  - fever, leukocytosis, tachycardia
  - peritoneal signs, early shock
  - see *Intestinal Ischemia*, GS28
- other:
  - perforation: secondary to ischemia and luminal distention
  - septicemia
  - hypovolemia (due to third spacing)

### Investigations

- radiological:
  - upright CXR or left lateral decubitus (LLD) to rule out free air, usually seen under the right hemidiaphragm
  - abdominal x-ray (3 views) to determine SBO vs. LBO vs. ileus (see Table 10)
    - ♦ if ischemic bowel look for: free air, pneumatosis, thickened bowel wall, air in portal vein, dilated small and large bowels, thickened or hose-like haustra (normally finger-like projections)
  - other:
    - ♦ most used: CT provides information on level of obstruction, severity, cause
      - important to r/o closed loop obstruction, especially in the elderly
    - ♦ less used: upper GI series/small bowel series for SBO (if no cause apparent, i.e. no hernias, no previous surgeries)
    - ♦ if suspect LBO, consider a rectal water-soluble (Gastrografin® for PO/PR; Hypaque® for IV) enema rather than barium enema (can thicken and cause complete obstruction)
    - ♦ may consider ultrasound or MRI in pregnant patients
- laboratory:
  - may be normal early in disease course
  - BUN, creatinine, hematocrit (hemoconcentration) to assess degree of dehydration
  - fluid, electrolyte abnormalities
  - amylase elevated
  - metabolic alkalosis due to frequent emesis
  - if strangulation: leukocytosis with left shift, lactic acidosis, elevated LDH (late signs)

### Treatment

- stabilize vitals, fluid and electrolyte resuscitation (with normal saline/Ringer's first, then with added potassium after fluid deficits are corrected)
- NG tube to relieve vomiting, prevent aspiration and decompress small bowel by prevention of further distention by swallowed air
- Foley catheter to monitor in/outs



#### MUST DO

Rule out CRC in constipated patient  
Send for TURP in patient with BPH (treat intra-abdominal hypertension)



#### Increased Risk of Perforation with Distention as seen on Abdo Imaging

- Small bowel  $\geq 3$  cm
- Distal colon  $\geq 6$  cm
- Proximal colon  $\geq 9$  cm
- Cecum  $\geq 12$  cm



Patients presenting with a SBO in setting of "virgin" abdomen should have surgery ASAP – EXCEPTION: malignant obstruction from history and imaging.

## Small Bowel Obstruction (SBO)



### Etiology

Table 11. Common Causes of SBO

Intraluminal	Intramural	Extramural
Intussusception Gallstones	Crohn's Radiation stricture Adenocarcinoma	Adhesions Incarcerated hernia Peritoneal carcinomatosis

### Treatment

- consider whether complete or partial obstruction, ongoing or impending strangulation, location and cause:
  - SBO with history of abdo/pelvic surgery → conservative management (likely to resolve) → surgery if no resolution in 48-72 h or complications
  - complete SBO, strangulation → urgent surgery after stabilizing patient with fluid resuscitation
  - SBO with no previous surgery and no evidence of carcinomatosis → operate
  - trial of medical management may be indicated in Crohn's, recurrent SBO, carcinomatosis
    - ♦ NGT decompression, GI rest, serial abdominal exams
  - special case: early postoperative SBO (within 30 d of abdominal surgery) – prolonged trial of conservative therapy may be appropriate, surgery is reserved for complications such as strangulation

### Prognosis

- mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%



In a non-virgin abdomen – adhesional SBOs resolve spontaneously with NG decompression 70% of time.



#### Top 3 Causes of SBO (in order)

**ABC**  
Adhesions  
Bulge (hernias)  
Cancer (neoplasms)



#### Causes of SBO

**SHAVING**  
Stricture  
Hernia  
Adhesions  
Volvulus  
Intussusception/IBD  
Neoplasm  
Gallstones



Never let the sun rise or set on a small bowel obstruction.



## Large Bowel Obstruction (LBO)

### Etiology

Table 12. Common Causes of LBO

Intraluminal	Intramural	Extramural
Constipation	Adenocarcinoma Diverticulitis IBD stricture Radiation stricture	Volvulus Adhesions

### Clinical Features (unique to LBO)

- open loop (10-20%) (safer):
  - incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical presentation similar to SBO
- closed loop (80-90%) (dangerous):
  - competent ileocecal valve, resulting in proximal and distal occlusions
  - massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

### Treatment

- surgical correction of obstruction (usually requires resection + temporary diverting colostomy)
- volvulus requires sigmoidoscopic or endoscopic decompression followed by operative reduction if unsuccessful
  - if successful, consider sigmoid resection on same admission
- cecal volvulus can be a true volvulus or a cecal 'bascule' – both need surgical treatment

### Prognosis

- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality



#### Top 3 Causes of LBO (in order)

- Cancer
- Diverticulitis
- Volvulus



In a patient with clinical LBO consider impending perforation when:

- Cecum  $\geq 12$  cm in diameter
- Tenderness present over cecum

## Colonic Pseudo-Obstruction

- aka paralytic ileus of large bowel

### Definition

- condition with symptoms of intestinal blockage without any physical signs of blockage

### Differential Diagnosis

- acute: toxic megacolon, trauma, postoperative (especially post orthopedic procedures with prolonged immobilization), neurologic disease, retroperitoneal disease, medications (narcotics, psychiatric)
- chronic: neurologic disease (enteric, central, peripheral nervous system), scleroderma

## Toxic Megacolon

### Pathogenesis

- extension of inflammation into smooth muscle layer causing paralysis
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

### Etiology

- inflammatory bowel disease (ulcerative colitis > Crohn's disease)
- infectious colitis: bacterial (*C. difficile*, *Salmonella*, *Shigella*, *Campylobacter*), viral (cytomegalovirus), parasitic (*E. histolytica*)
- volvulus, diverticulitis, ischemic colitis, obstructing colon cancer are rare causes

### Clinical Features

- infectious colitis usually present for >1 wk before colonic dilatation
- diarrhea  $\pm$  blood (but improvement of diarrhea may portend onset of megacolon)
- abdominal distention, tenderness,  $\pm$  local/general peritoneal signs (suggest perforation)
- triggers: hypokalemia, constipating agents (opioids, antidiarrheals, loperamide, anticholinergics), barium enema, colonoscopy



Colon is MEGA and patient is TOXIC.



**Diagnostic Criteria**

- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon
- **three of:** fever, HR >120, WBC >10.5, anemia
- **one of:** fluid and electrolyte disturbances, hypotension, altered LOC

**Investigations**

- CBC (leukocytosis with left shift, anemia from bloody diarrhea), electrolytes, elevated CRP, ESR
- metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease

**Treatment**

- NPO, NG tube, stop constipating agents, correct fluid and electrolyte abnormalities, transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis, anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD, metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management):
  - worsening or persisting toxicity or dilation after 48-72 h
  - severe hemorrhage, perforation
  - high lactate and WBC especially for *C. difficile*
- procedure: subtotal colectomy + end ileostomy (may be temporary, with second operation for re-anastomosis later)



Use caution when giving antidiarrheals, especially with bloody diarrhea.

**Prognosis**

- average 25-30% mortality

## Paralytic Ileus

**Pathogenesis**

- temporary paralysis of the myenteric plexus

**Associations**

- postoperative, intra-abdominal sepsis, medications (opiates, anesthetics, psychotropics), electrolyte disturbances ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ), *C. difficile*, inactivity

**Treatment**

- NG decompression, NPO, fluid resuscitation, correct causative abnormalities (e.g. sepsis, medications, electrolytes), consider TPN for prolonged ileus
- post-op: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d
- current interest in novel therapies such as gum chewing and pharmacologic therapy (opioid antagonists)

## Ogilvie's Syndrome

- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- arises in bedridden patients with serious extraintestinal illness or trauma
- exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic deprivation to colon, unopposed parasympathetic tone, and interruption of sacral parasympathetic tone to distal bowel
- first presents with abdominal distention (>90%) ± tenderness
- later symptoms mimic true obstruction

**Associations**

- most common: trauma, infection, cardiac (MI, CHF)
- disability (long term debilitation, chronic disease, bed-bound nursing home patients, paraplegia), drugs (narcotic use, laxative abuse, polypharmacy), other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, diffuse carcinomatosis)

**Investigations**

- AXR: cecal dilatation – if diameter  $\geq 12$  cm, increased risk of perforation

**Treatment**

- treat underlying cause
- NPO, NG tube
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical decompression (ostomy/resection) uncommon
- surgery (extremely rare): if perforation, ischemia or failure of conservative management

**Prognosis**

- most resolve with conservative management

# Intestinal Ischemia

## Etiology

- acute:
  - arterio-occlusive mesenteric ischemia (AOMI)
    - ♦ thrombotic, embolic, extrinsic compression (e.g. strangulating hernia)
  - non-occlusive mesenteric ischemia (NOMI)
    - ♦ mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  - mesenteric venous thrombosis (MVT)
    - ♦ consider hypercoagulable state (i.e. rule out malignancy), DVT (prevents venous outflow)
- chronic: usually due to atherosclerotic disease – look for CVD risk factors

## Clinical Features

- acute: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, sepsis
- chronic: postprandial pain, fear of eating, weight loss
- common sites: superior mesenteric artery (SMA) supplied territory, “watershed” areas of colon – splenic flexure, left colon, sigmoid colon

## Investigations

- laboratory: leukocytosis (non-specific), lactic acidosis (late finding)
  - amylase, LDH, CK, ALP can be used to observe progress
  - hypercoagulability workup if suspect venous thrombosis
- AXR: portal venous gas, intestinal pneumatosis, free air if perforation
- contrast CT: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, pneumatosis
- CT angiography is the gold standard for acute arterial ischemia

## Treatment

- fluid resuscitation, correct metabolic acidosis, NPO, NG decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
- exploratory laparotomy
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, percutaneous transluminal angioplasty ± stent
- segmental resection of necrotic intestine:
  - assess extent of viability; if extent of bowel viability is uncertain, a second look laparotomy 12-24 h later is mandatory



Pain “out of keeping with physical findings” is the hallmark of early intestinal ischemia.



An acute abdomen + metabolic acidosis is bowel ischemia until proven otherwise.

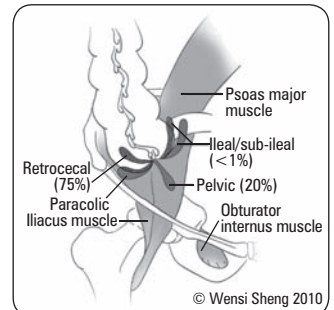


Figure 14. Appendix anatomy



## Modified Alvarado Score for Acute Appendicitis

- 1 point per:
  - Migratory right iliac fossa pain (1 point)
  - Anorexia (1 point)
  - Nausea/vomiting (1 point)
  - Tenderness in right iliac fossa (2 points)
  - Rebound tenderness in right iliac fossa (1 point)
  - Fever  $>37.5^{\circ}\text{C}$  (1 point)
  - Leukocytosis (2 points)
- 0-3 = low risk, discharge to return if no improvement
- 4-6 = moderate risk, admit, observe, repeat examinations
- Male 7-9 = appendectomy
- Female (not pregnant) 7-9 = diagnostic laparoscopy ± appendectomy



## McBurney's Sign

Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side.



## Laparoscopic vs. Open Appendectomy

### Laparoscopic Surgery

- Wound infection less likely
- Intra-abdominal abscesses 2 times more likely
- Reduced pain on POD #1
- Reduced hospital stay by 1.1 d
- Sooner return to normal activity, work and sport
- Costs outside hospital are reduced

### Open Surgery

- Shorter duration of surgery
- Lower operation costs

### Overview

Diagnostic laparoscopy and laparoscopic appendectomy appear to be advantageous over open appendectomy, particularly for young female patients and obese patients.

Cochrane DB Syst Rev 2010;10:CD001546

# Appendix



## Appendicitis

## Epidemiology

- 6% of population, M>F
- 80% between 5-35 yr of age

## Pathogenesis

- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology:
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecolith, obstructing neoplasm
  - other causes: parasites, foreign body

## Clinical Features

- most reliable feature is progression of signs and symptoms
- low grade fever ( $38^{\circ}\text{C}$ ), rises if perforation
- abdominal pain then anorexia, nausea and vomiting
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney's point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
  - McBurney's sign

- signs:
  - inferior appendix: McBurney's sign (see GS28), Rovsing's sign (palpation pressure to left abdomen causes McBurney's point tenderness)
  - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
  - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)
- complications:
  - perforation (especially if >24 h duration)
  - abscess, phlegmon

### Investigations

- laboratory:
  - mild leukocytosis with left shift (may have normal WBC counts)
  - higher leukocyte count with perforation
  - $\beta$ -hCG to rule out ectopic pregnancy
  - urinalysis
- imaging:
  - upright CXR, AXR: usually nonspecific – free air if perforated (rarely), calcified fecolith, loss of psoas shadow, RLQ ileus
  - ultrasound: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/ NPV/PPV 98%)
  - CT scan: thick wall, appendicolith, inflammatory changes – overall accuracy 94-100%, optimal investigation

### Treatment

- hydrate, correct electrolyte abnormalities
- surgery (gold standard, 20% mortality with perforation especially in elderly) + antibiotic coverage
- if localized abscess (palpable mass or large phlegmon on imaging and often pain >4-5 d), consider radiologic drainage + antibiotics x 14 d  $\pm$  interval appendectomy in 6 wk (controversial)
- appendectomy:
  - laparoscopic vs. open (see sidebar)
  - complications: spillage of bowel contents, pelvic abscess, enterocutaneous fistula
  - perioperative antibiotics:
    - ♦ cefazolin + metronidazole (no post-op antibiotic unless perforated)
    - ♦ other choices: 2nd/3rd generation cephalosporin for aerobic gut organisms
- colonoscopy in the elderly to rule out other etiology (neoplasm)

### Prognosis

- mortality rate: 0.08% (non-perforated), 0.5% (perforated appendicitis)



#### Effect of Delay to Operation on Outcomes in Adults with Acute Appendicitis

*Arch Surg* 2010;145:886-892

**Purpose:** To examine the effect of delay to appendectomy on morbidity and mortality among adults with appendicitis.

**Method:** Retrospective cohort study with the main exposure being time to operation, and main outcomes being 30-d overall morbidity and serious morbidity/mortality.

**Results:** Of 32,782 patients in the study, 75.2%, 15.1%, and 9.8% underwent surgeries within 6 h, 6-12 h, and >12 h of admission, respectively. Differences in operative duration and length of postoperative stay were statistically significant but not clinically meaningful. No significant differences were observed in adjusted overall morbidity or serious morbidity/mortality. Duration from surgical admission to anesthesia induction was not predictive in regression models for either outcomes.

**Conclusions:** Delay of appendectomy for acute appendicitis among adults does not adversely affect outcomes.



#### Antibiotics versus Placebo for Prevention of Postoperative Infection after Appendectomy

*Cochrane DB Syst Rev* 2005;3:CD001439

**Purpose:** To determine the effectiveness of antibiotics against postoperative infections after appendectomy.

**Method:** Meta-analysis of randomized controlled trials (RCTs) and controlled clinical trials (CCTs), on both adults and children, in which any antibiotic regime was compared to placebo in patients undergoing appendectomy for suspected appendicitis. The main outcomes of interest were wound infection, intra abdominal abscess, length of hospital stay, and mortality.

**Results:** 45 studies (n = 9576) were included. Treatment with antibiotics decreased wound infection and abscess rates.

**Conclusion:** Various prophylactic antibiotic regimens are effective in preventing postoperative complications after appendectomy.

## Tumours of the Appendix

### CARCINOID TUMOURS (most common type)

- see *Tumours of Small Intestines: Carcinoid section*, GS21

### ADENOCARCINOMA

- 50% present as acute appendicitis
- spreads rapidly to lymph nodes, ovaries, and peritoneal surfaces
- treatment: right hemicolectomy

### OTHER

- malignant mucinous cystadenocarcinoma

## Inflammatory Bowel Disease (IBD)

- see *Gastroenterology*, G19

### Principles of Surgical Management

- can alleviate symptoms, address complications, improve quality of life
- conserve bowel: resect as little as possible to avoid short gut syndrome
- perioperative management:
  - optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  - hold immunosuppressive therapy pre-op, provide pre-op stress dose of corticosteroid if patient had recent steroid therapy, taper steroids post-op
  - DVT prophylaxis: heparin (IBD patients at increased risk of thromboembolic events)



## Crohn's Disease

- see [Gastroenterology](#), G20

### Treatment

- surgery is NOT curative, but over lifetime ~70% of Crohn's patients will have surgery
- indications for surgical management:
  - failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), perianal disease
- surgical procedures:
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, fistula
    - ♦ resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

### Complications of Treatment

- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

### Prognosis

- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr



#### Crohn's 3 Major Patterns

- Ileocecal 40% (RLQ pain, fever, weight loss)
- Small intestine 30% (especially terminal ileum)
- Colon 25% (diarrhea)



#### Findings in Crohn's

- "Cobblestoning" on mucosal surface due to edema and linear ulcerations
- "Skip lesions": normal mucosa in between
- "Creeping fat": mesentery infiltrated by fat
- Granulomas: 25-30%
- Barium enema: "lead-pipe appearance"

## Ulcerative Colitis

- see [Gastroenterology](#), G22

### Treatment

- indications for surgical management:
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per year after 10 yr of disease)
- surgical procedures:
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
  - in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

### Complications of Treatment

- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

### Prognosis

- mortality: 5% over 10 yr
- total proctocolectomy will completely eliminate risk of cancer
- perforation of the colon is the leading cause of death from ulcerative colitis



#### Findings in Ulcerative Colitis

- Patients usually present with diarrhea (± blood in their stool)
- Associated symptoms include colicky abdominal pain, urgency, tenesmus and incontinence
- Presence of extraintestinal manifestations
- Endoscopically, there is loss of ascaral markings, erythema, granularity of mucosa, petechiae, exudates, edema, erosions, and spontaneous bleeding
- Biopsy features included crypt abscesses, crypt branching, shortening and disarray, and crypt atrophy
- Inflammation is continuous, and usually involves rectum



Both ulcerative colitis and Crohn's disease present with an increased risk of colorectal cancer.

## Diverticular Disease



### Definitions

- diverticulum: abnormal sac-like protrusion from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

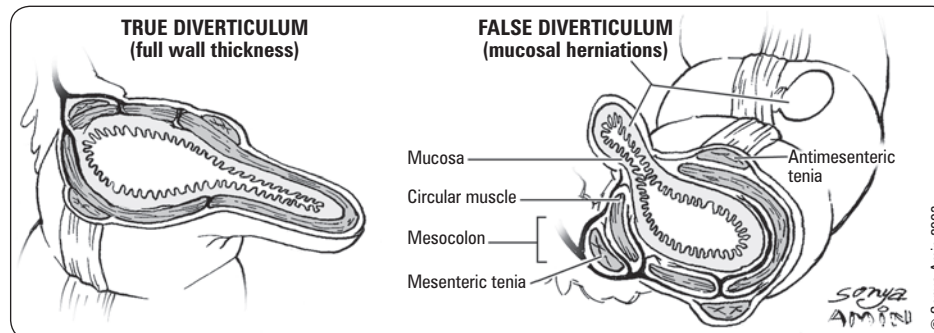


Figure 15. Diverticular disease – cross-sections of true and false diverticuli

## Diverticulosis

### Epidemiology

- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

### Pathogenesis

- risk factors:
  - lifestyle: low-fibre diet (predispose to motility abnormalities and higher intraluminal pressure) inactivity, obesity
  - muscle wall weakness from aging and illness (e.g. Ehler-Danlos, Marfan's)
- high intraluminal pressures cause outpouching to occur at point of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer, therefore increased risk of hemorrhage

### Clinical Features

- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications:
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive lower GI bleeds
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, abdominal pain

### Treatment

- uncomplicated diverticulosis: high fibre, education
- diverticular bleed:
  - initially work up and treat as any lower GI bleed
  - if hemorrhage does not stop, resect involved region

## Diverticulitis

### Epidemiology

- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

### Pathogenesis

- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula or obstruction can ensue
- poor containment results in free perforation and peritonitis



#### Diverticulosis vs. Diverticulitis

Diverticulosis represents the presence of diverticuli (bulging pouches) within the colonic wall, whereas diverticulitis is the inflammation of one or more diverticuli.



### Clinical Features

- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, nausea, vomiting, urinary symptoms (with adjacent inflammation)
- complications (25% of cases):
  - abscess: palpable tender abdominal mass
  - fistula: colovesical (most common), coloenteric, colovaginal, colocutaneous
  - colonic obstruction: due to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
    - ♦ recurrent attacks rarely lead to peritonitis
- low-grade fever, mild leukocytosis common,
- occult or gross blood in stool rarely coexist with acute diverticulitis

### Investigations

- AXR, upright CXR:
  - localized diverticulitis (ileus, thickened wall, SBO, partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- CT scan (test of choice): very useful for assessment of severity and prognosis
  - 97% sensitive, 99% specific
  - increased soft tissue density within pericolic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- Hypaque® (water soluble) enema – safe (under low pressure):
  - saw-tooth pattern (colonic spasm)
  - may show site of perforation, abscess cavities or sinus tracts, fistulas
- elective evaluations: establish extent of disease and rule out other diagnoses (polyps, malignancy) after resolution of acute episode
  - colonoscopy or barium enema and flexible sigmoidoscopy

### Treatment

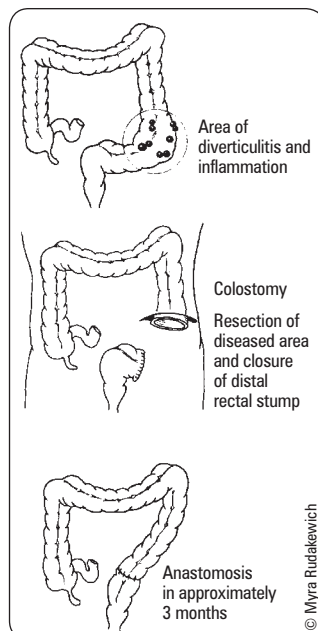
- uncomplicated: conservative management
- outpatient: clear fluids only until improvement and antibiotics (e.g. ciprofloxacin and metronidazole) 7-10 d to cover gram negative rods and anaerobes (e.g. *B. fragilis*)
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, fail to improve outpatient management
- treat with NPO, IVF, IV antibiotics (e.g. IV ceftriaxone + metronidazole, ampicillin, gentamicin)
- indications for surgery:
  - unstable patient with peritonitis
  - Hinchey stage 3-4 (see Table 13)
  - after 1 attack if: (a) immunosuppressed, (b) abscess needing percutaneous drainage
  - consider after 2 or more attacks, recent trend is toward conservative management of recurrent mild/moderate attacks
  - complications: generalized peritonitis, free air, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
- surgical procedures:
  - for emergency or complex cases: Hartmann procedure: colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo (see Figure 16)
  - elective cases or minimal contamination of the abdominal cavity: consider colon resection + primary anastomosis

### Prognosis

- mortality rates: 6% for purulent peritonitis, 35% for fecal peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

**Table 13. Hinchey Staging and Treatment for Diverticulitis**

Hinchey Stage	Description	Acute treatment
1	Phlegmon/small pericolic abscess	Medical
2	Large abscess/fistula	Abscess drainage, resection ± primary anastomosis
3	Purulent peritonitis (ruptured abscess)	Hartmann procedure
4	Feculent peritonitis	Hartmann procedure



**Figure 16. Hartmann procedure**



# Colorectal Neoplasms

## Colorectal Polyps

### Definition

- polyp: protuberance into the lumen of normally flat colonic mucosa
- sessile (flat) or pedunculated (on a stalk) (see Figure 17)

### Epidemiology

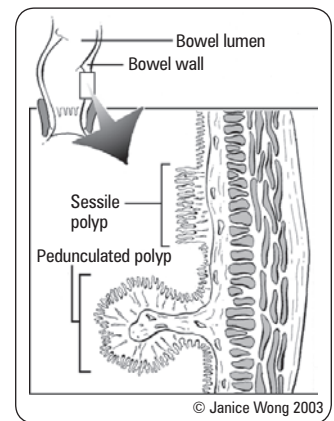
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70

### Clinical Features

- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, mucus
- usually detected during routine endoscopy or familial/high risk screening

### Pathology

- non-neoplastic:
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, carcinoids
- neoplastic:
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
    - ♦ malignant risk due to associated adenomas (large bowel)
    - ♦ low malignant potential → most spontaneously regress or autoamputate
  - adenomas: premalignant, often carcinoma in situ:
    - ♦ some may contain invasive carcinoma ("malignant polyp" – 3-9%): invasion into muscularis
    - ♦ malignant potential: villous > tubulovillous > tubular (see Table 14)



**Figure 17. Sessile and pedunculated polyps**

**Table 14. Characteristics of Tubular vs. Villous Polyps**

	Tubular	Villous
<b>Incidence</b>	Common (60% to 80%)	Less common (10%)
<b>Size</b>	Small (<2 cm)	Large (usually >2 cm)
<b>Attachment</b>	Pedunculated	Sessile
<b>Malignant Potential</b>	Lower	Higher
<b>Distribution</b>	Even	Left-sided predominance

### Investigations

- colonoscopy is the gold standard for diagnosis and treatment of colonic polyps
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscope if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy

### Treatment

- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- surgical resection for those invading into muscularis (high risk of malignancy) and those too large to remove endoscopically
- follow-up endoscopy 1 yr later, then every 3-5 yr



## Familial Colon Cancer Syndromes

### FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

#### Pathogenesis

- autosomal dominant (AD) inheritance, mutation in adenomatous polyposis coli (APC) gene on chromosome 5q21

#### Clinical Features

- hundreds to thousands of colorectal adenomas usually by age 20 (by 40s in attenuated FAP)
- extracolonic manifestations:
  - carcinoma of small bowel (i.e. polyps in colon), bile duct, pancreas, stomach, thyroid, adrenal, small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
  - virtually 100% lifetime risk of colon cancer (because of number of polyps)

- variants:
  - Gardner's syndrome: FAP + extraintestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
  - Turcot syndrome: FAP + CNS tumours (childhood cerebellar medulloblastoma)

### Investigations

- genetic testing (80-95% sensitive, 99-100% specific) (see sidebar)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy and consider surgery (see Figure 16); consider upper endoscopy to evaluate for periampullary tumours

### Treatment

- surgery indicated by age 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

## HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC) – LYNCH SYNDROME

### Pathogenesis

- AD inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1) resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all colorectal cancers

### Clinical Features

- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr, lifetime risk 70-80% (M>F)
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

### Diagnosis

- Amsterdam Criteria:
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr old
  - FAP is excluded
- genetic testing (80% sensitive) – colonoscopy mandatory even if negative
  - refer for genetic screening individuals who fulfill EITHER the Amsterdam Criteria (as above) OR the revised Bethesda Criteria (see sidebar)
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

### Treatment

- total colectomy and ileorectal anastomosis with annual proctoscopy



#### Referral Criteria for Genetic Screening for APC

- To confirm the diagnosis of FAP (in patients with  $\geq 100$  colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are  $\geq 10$  yr old)
- To confirm the diagnosis of attenuated FAP (in patients with  $\geq 20$  colorectal adenomas)



#### Revised Bethesda Criteria for HNPCC and Microsatellite Instability (MSI)

Tumours from individuals should be tested for MSI in the following situations:

- Colorectal cancer diagnosed in a patient who is less than 50 yr of age.
- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours, regardless of age.
- Colorectal cancer with the MSI-H histology diagnosed in a patient who is less than 60 yr of age.
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under age 50 yr.
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age.



Elderly persons who present with iron-deficiency anemia should be investigated for colon cancer.



#### Staging for CRC

- I T1,2 N0 M0
- II T3,4 N0 M0
- III TxN+ M0
- IV TxNxM1



#### 5-year Survival Rates for CRC

Stage	Colon	Rectum
I	74%	74%
IIA	67%	64%
IIB	59%	52%
IIC	37%	32%
IIIA	73%	74%
IIIB	46%	45%
IIIC	28%	33%
IV	6%	6%

## Colorectal Carcinoma (CRC)

### Epidemiology

- 4th most common cancer (after lung, prostate and breast), 2nd most common cause of cancer death

### Risk Factors

- most patients have no specific risk factors
- age >50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, family history of CRC
- colonic conditions:
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - previous colorectal cancer (also gonadal or breast)
- diet (increased fat, red meat, decreased fibre) and smoking
- diabetes mellitus and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

### Pathogenesis

- adenoma-carcinoma sequence; rarely arise *de novo*

**Clinical Features** (see Table 15)

- often asymptomatic
- hematochezia/melena, abdominal pain, change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread:
  - direct extension, lymphatic, hematogenous (liver most common, lung, bone, brain; tumour of distal rectum → IVC → lungs)
  - peritoneal seeding: ovary, Blumer's shelf (pelvic cul-de-sac)

**Table 15. Clinical Presentation of CRC**

	Right Colon	Left Colon	Rectum
<b>Frequency</b>	25%	35%	30%
<b>Pathology</b>	Exophytic lesions with occult bleeding	Annular, invasive lesions	Ulcerating
<b>Symptoms</b>	Weight loss, weakness, rarely obstruction	Constipation ± overflow (alternating bowel patterns), abdominal pain, decreased stool caliber, rectal bleeding	Obstruction, tenesmus, rectal bleeding
<b>Signs</b>	Fe-deficiency anemia, RLQ mass (10%)	BRBPR, LBO	Palpable mass on DRE, BRBPR

**Investigations**

- colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema ("apple core" lesion) + sigmoidoscopy
- if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy
- laboratory: CBC, urinalysis, liver enzymes, liver function test, carcinoembryonic antigen (CEA) (preoperative for baseline, >5 ng/mL have worse prognosis)
- staging (see Table 16 and sidebar): chest, abdominal and pelvis CT; bone scan, CT head only if lesions suspected
- rectal cancer: pelvic MRI or endorectal ultrasound to determine T and N stage

**Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)**

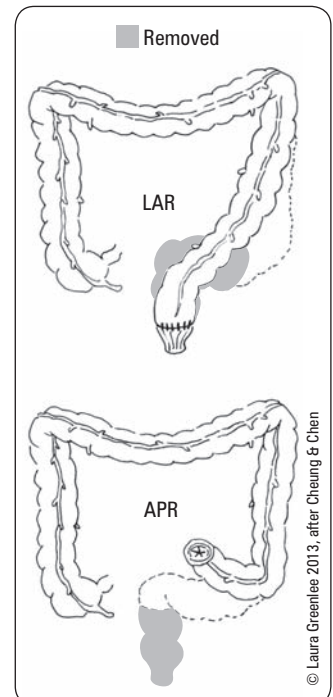
Primary Tumour (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
T0 No primary tumour found	N0 No regional node involvement	M0 No distant metastasis
Tis Carcinoma in situ	N1 Metastasis in 1-3 regional nodes	M1 Distant metastasis
T1 Invasion into submucosa	N2 Metastasis in 4 or more regional nodes	
T2 Invasion into muscularis propria		
T3 Invasion through muscularis propria and into serosa		
T4 Invasion into adjacent structures or organs		

**Treatment**

- **colon cancer**
  - wide surgical resection of lesion and regional lymphatic drainage; usually colectomy with primary anastomosis
    - ♦ curative: wide resection of lesion (5 cm margins) with nodes and mesentery
    - ♦ palliative: if distant spread, local control for hemorrhage or obstruction
    - ♦ care is taken to not spread tumour by unnecessary palpation
    - ♦ cancer-bearing portion of colon is removed according to vascular distribution of segment
  - adjuvant chemotherapy (5-FU or oral capecitabine with oxaliplatin) can be considered for stage II or III
- **rectal cancer**
  - choice of operation depends on individual case. Types of operations (see Figure 18):
    - ♦ low anterior resection of rectum (LAR): curative procedure of choice if adequate distal margins; uses technique of total mesorectal excision
    - ♦ abdominoperineal resection of rectum (APR): if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus – permanent end colostomy required
    - ♦ local excision: for select T1 lesions only
    - ♦ palliative procedures: electrocoagulation or laser photocoagulation for unresectable cancers for symptom relief
  - adjuvant therapy:
    - ♦ combined neoadjuvant chemoradiation therapy followed by postoperative adjuvant chemotherapy for stage II and III

**Follow-Up**

- currently there are no data suggesting optimal follow-up
- combination of periodic CT chest/abdo/pelvis, CEA and colonoscopy is recommended
- CEA to monitor for initial response to treatment, and to assess for recurrence q3mo (not a screening test)
- intensive follow-up improves overall survival in low risk patients

**Figure 18. APR vs. LAR**

APR removes distal sigmoid colon, rectum and anus, permanent end colostomy required.

LAR removes distal sigmoid and rectum with anastomosis of distal colon to anus.



**Preoperative versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial after a Median Follow-Up of 11 Years**

*J Clin Oncol* 2012; 30: 1926–1933.

**Background:** The CAO/ARO/AIO-94 trial (published 2004) recommended preoperative chemoradiotherapy (CRT) as standard treatment for locally advanced rectal cancer. However, no survival benefit was shown after median follow-up of 46 mo, and this study reports long-term effects.

**Methods:** Patients with stage II to III rectal cancer (n=799) were randomly assigned to preop (n=404) or postop CRT (n=395) with fluorouracil (FU), radiation, and adjuvant FU chemotherapy, in addition to total mesorectal excision surgery. Follow-up was designed to assess long-term overall survival as the primary end point; and cumulative incidence of local and distant relapses and disease-free survival as secondary end points.

**Results:** 10-yr incidence of local relapse was significantly lower in the preop CRT group than in the postop group (7.1% vs. 10.1%, p=0.048). Overall survival at 10 yr was similar at ~60% for patients treated with preop or postop CRT (p=0.85). Disease-free survival rates at 10 yr were similar at ~68% for patients treated with preop or postop CRT (p=0.54). No significant difference was detected for 10-yr incidence of distant metastases (preop CRT 29.8% vs. postop CRT 29.6%, p=0.9).

**Conclusion:** There is long-term reduction in local recurrence of stage II to III rectal cancer with preoperative chemotherapy, but no improvement in overall survival or distant recurrence of disease.

## Other Conditions of the Large Intestine

### Angiodysplasia

#### Definition

- vascular anomaly: focal submucosal venous dilatation and tortuosity

#### Clinical Features

- most frequently in right colon of patients >60 yr old
- bleeding typically intermittent, rarely massive, not usually hypotensive (melena, anemia, guaiac positive stools)

#### Investigations

- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

#### Treatment

- none if asymptomatic
- cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

### Volvulus

#### Definition

- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), splenic flexure (2%)
- 5-10% of large bowel obstruction; 25% of intestinal obstruction during pregnancy

#### Risk Factors

- age (50% of patients >70 yr: stretching/elongation of bowel with age is a predisposing factor)
- high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, institutionalization (less frequent evacuation of bowels)
- congenital hypermobile cecum

#### Clinical Features

- symptoms due to bowel obstruction (see GS24) or intestinal ischemia (see GS28)
- colicky abdominal pain, persistence of pain between spasms, abdominal distention, vomiting

#### Investigations

- AXR (classic findings): "omega", "bent inner-tube", "coffee-bean" signs
- barium/Gastrografin® enema: "ace of spades" (or "bird's beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT

#### Treatment

- initial supportive management (same as initial management for bowel obstruction (see GS24))
- cecum:
  - nonsurgical:
    - ♦ may attempt colonoscopic detorsion and decompression
  - surgical:
    - ♦ right colectomy + ileotransverse colonic anastomosis
- sigmoid:
  - nonsurgical:
    - ♦ decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
    - ♦ subsequent elective surgery recommended (50-70% recurrence)
  - surgical: Hartmann procedure (if urgent)
    - ♦ indications: strangulation, perforation or unsuccessful endoscopic decompression



#### Cecal Volvulus

AXR: Central cleft of "coffee bean" sign points to RLQ.



#### Sigmoid Volvulus

AXR: Central cleft of "coffee bean" sign points to LLQ.

Barium enema: "ace of spades" or "birds beak" sign.

## Fistula

### Definition

- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, entero-enteric)

### Etiology

- foreign object erosion (e.g. gallstone, graft)
- inflammatory states (e.g. infection, IBD (especially Crohn's), diverticular disease)
- iatrogenic/surgery (e.g. postoperative anastomotic leak, radiation)
- congenital, trauma
- neoplastic

### Investigations

- ultrasound, CT scan, fistulogram
- measure amount of drainage from fistula

### Treatment

- decrease secretion: octreotide/somatostatin/omeprazole
- surgical intervention: dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis



#### Why Fistulae Stay Open

##### FRIENDO

- Foreign body
- Radiation
- Infection
- Epithelialization
- Neoplasm
- Distal obstruction (most common)
- Others: increased flow; steroids (may inhibit closure, usually will not maintain fistula)

## Stomas

### Definition

- an opening of the GI tract onto the surface of the abdomen wall

### Ileostomy

- usually positioned in RLQ; ileum is brought through rectus abdominus muscles
- indications: after colectomy for ulcerative colitis, in some cases of Crohn's disease or familial polyposis
- conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
- continent ileostomy: reservoir is constructed from distal ileum, emptied by inserting catheter into stoma several times a day; rarely used, has mostly been replaced by ileal pouch anal anastomosis

### Colostomy

- indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
- colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
- most common permanent colostomy is a sigmoid colostomy – expels stool once per day, no appliance required
- chronic paracolostomy hernia is a common complication

### Complications (10%)

- obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
- peri-ileostomy abscess and fistula
- skin irritation
- prolapse or retraction
- diarrhea (excessive output)

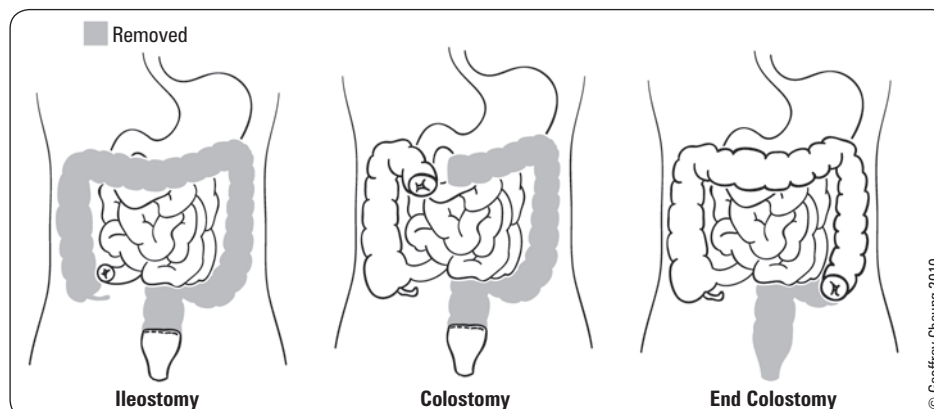


Figure 19. Ostomies



#### Colostomy/Ileostomy

- Connection of proximal limb of colon or ileum to abdominal wall skin

#### Mucous Fistula

- Connection of distal limb of colon to abdominal wall skin

#### Ileal Conduit

- Connection of bowel to ureter proximally and abdominal wall distally to drain urine

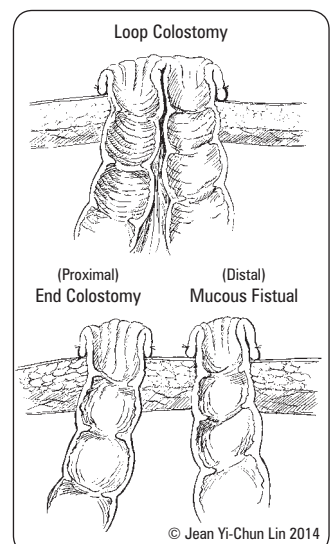


Figure 20. End vs. loop colostomy



# Anorectum

## Hemorrhoids

### Etiology

- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
  - internal: superior hemorrhoidal veins, above dentate line, portal circulation
  - external: inferior hemorrhoidal veins, below dentate line, systemic circulation

### Risk Factors

- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal hypertension, heavy lifting

### Clinical Features and Treatment

- internal hemorrhoids:
  - engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  - PAINLESS rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, rectal fullness:
    - 1st degree:** bleed but do not prolapse through the anus
      - treatment: high fibre/bulk diet, sitz baths, steroid cream, pamoxyne (Anusol®), rubber band ligation, sclerotherapy, photocoagulation
    - 2nd degree:** bleed, prolapse with straining, spontaneous reduction
      - treatment: rubber band ligation, photocoagulation
    - 3rd degree:** bleed, prolapse, requires manual reduction
      - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
    - 4th degree:** bleed, permanently prolapsed, cannot be manually reduced
      - treatment: closed hemorrhoidectomy
- external hemorrhoids:
  - dilated venules usually mildly symptomatic
    - PAIN after bowel movement, associated with poor hygiene
    - medical treatment: dietary fibre, stool softeners, steroid cream (short course), pamoxyne (Anusol®), avoid prolonged straining
  - thrombosed hemorrhoids are very painful:
    - resolve within 2 wk, may leave excess skin = perianal skin tag
    - treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment



Always rule out more serious causes (e.g. colon CA) in a person with hemorrhoids and rectal bleeding.

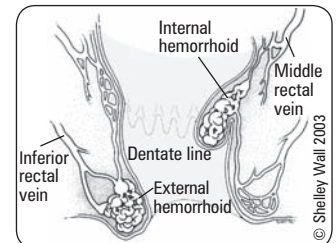


Figure 21. Hemorrhoids



Band ligation can be done as outpatient.



External hemorrhoids will often recur.

Table 17. Signs and Symptoms of Internal vs. External Hemorrhoids

Internal Hemorrhoids	External Hemorrhoids
Painless bright red blood per rectum	Sudden severe perianal pain
Rectal fullness or discomfort	Perianal mass
Mucus discharge	

## Anal Fissures

### Definition

- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline, 10% anterior midline
- if off midline: consider other possible causes such as IBD, STIs, TB, leukemia or anal carcinoma
- repetitive injury cycle after first tear:
  - sphincter spasm occurs preventing edges from healing and leads to further tearing
  - ischemia may ensue and contribute to chronicity

### Etiology

- forceful dilation of anal canal: large, hard stools and irritant diarrheal stools
- tightening of anal canal secondary to nervousness/pain leads to further tearing
- others: habitual use of cathartics, childbirth

### Clinical Features

- acute fissure:
  - very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - treatment is conservative: stool softeners, bulking agent, sitz baths (heals 90%)
- chronic fissure (anal ulcer):
  - triad: fissure, sentinel skin tags, hypertrophied papillae



- treatment:
  - ♦ stool softeners, bulking agents, sitz baths
  - ♦ topical nitroglycerin or nifedipine: increases local blood flow, promoting healing and relieves sphincter spasm
  - ♦ lateral internal anal sphincterotomy (most effective): objective is to relieve sphincter spasm → increases blood flow and promotes healing; but 5% chance of fecal incontinence therefore not commonly done
- alternative treatment:
  - ♦ botulinum toxin: inhibits release of acetylcholine (ACh), reducing sphincter spasm

## Anorectal Abscess

### Definition

- infection in one or more of the anal spaces
- usually bacterial infection of blocked anal gland at the dentate line
  - *E. coli*, *Proteus*, *Streptococci*, *Staphylococci*, *Bacteroides*, anaerobes

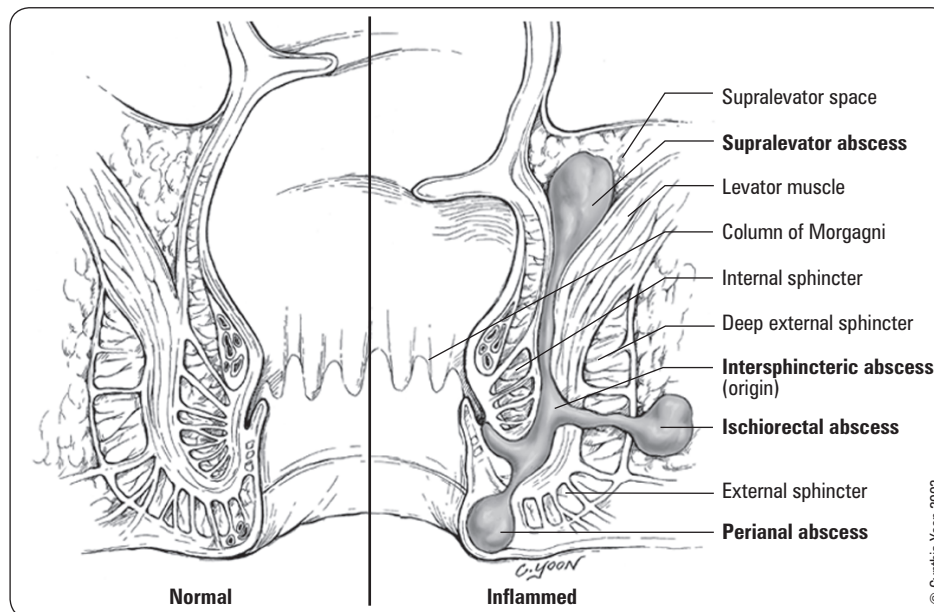


Figure 22. Different types of perianal abscesses

### Clinical Features

- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralelevator) or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

### Treatment

- incision and drainage
  - curative in 50% of cases
  - 50% develop anorectal fistulas
- may require antibiotics if diabetic, heart murmur or cellulitis



Recurrent perianal abscesses is associated with Crohn's disease.



Antibiotics are not typically helpful in the treatment of perianal abscesses.

## Fistula-In-Ano

### Definition

- anal fistula from rectum to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

### Etiology

- see *Fistula*, GS37
- same perirectal process as an anal abscess, therefore usually associated with an abscess
- other causes: post-op, trauma, anal fissure, malignancy, radiation proctitis

### Clinical Features

- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract

**Treatment**

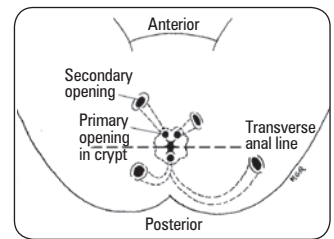
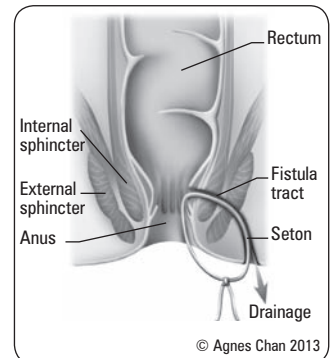
- identification:
  - internal opening:
    - ♦ Goodsall's rule
      - fistulas originating anterior to transverse line through the anus will course straight ahead and exit anteriorly, whereas those with exit posterior to the transverse line will have a curved tract and originate in the midline
  - fistulous tract:
    - ♦ probing or fistulography under anesthesia
- surgery:
  - fistulotomy: unroof tract from external to internal opening, allow drainage, heals by secondary intention
  - low lying fistula (does not involve external sphincter) → primary fistulotomy
  - high lying fistula (involves external sphincter) → staged fistulotomy with Seton suture placed through tract:
    - ♦ promotes drainage
    - ♦ promotes fibrosis and decreases incidence of incontinence
    - ♦ delineates anatomy
    - ♦ usually done to spare muscle cutting

**Postoperative**

- sitz baths, irrigation and packing to ensure healing proceeds from inside to outside

**Complications**

- recurrence
- rarely fecal incontinence

**Figure 23. Goodsall's rule****Figure 24. Fistulotomy**

## Pilonidal Disease

**Definition**

- chronic recurring abscess or chronic draining sinus in sacrococcygeal area

**Epidemiology**

- occurs most frequently in young men age 15-40 yr; rare in >50 yr

**Etiology**

- obstruction of the hair follicles in this area → formation of cysts, sinuses or abscesses

**Clinical Features**

- asymptomatic until acutely infected, then pain/tenderness, purulent discharge, inspissated hair

**Treatment**

- acute abscess:
  - I&D (often performed by primary care doctors)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery:
  - indication: failure of healing after I&D, recurrent disease, complex disease
  - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention, primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

## Rectal Prolapse

**Definition**

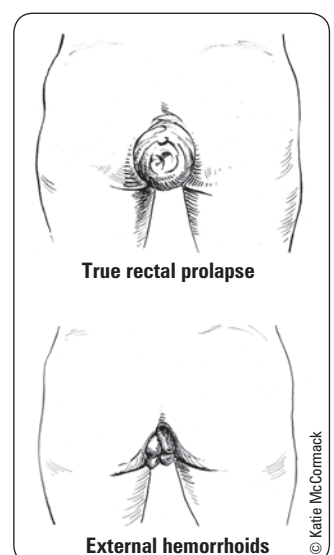
- protrusion of some or all of rectal mucosa through external anal sphincter

**Epidemiology**

- extremes of ages: <5 yr old and >5th decade
- 85% women

**Etiology**

- lengthened attachment of rectum secondary to constant straining
- 2 types:
  - I. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  - II. true/complete (most common): full thickness extrusion of rectal wall, concentric folds in:
    - ♦ first degree: prolapse includes mucocutaneous junction
    - ♦ second degree: without involvement of mucocutaneous junction
    - ♦ third degree (internal intussusception): prolapse is internal, concealed, or occult

**Figure 25. Rectal prolapse (true vs. false)**

**Risk Factors**

- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility

**Clinical Features**

- extrusion of mass with increased intra-abdominal pressure:
  - straining, coughing, laughing, Valsalva
- difficulty in bowel regulation:
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration and constant soiling
- may be associated with urinary incontinence or uterine prolapse

**Treatment**

- Type I:
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- Type II:
  - conservative: reduce if possible
  - surgery: abdominal, perineal, transsacral approaches

## Anal Neoplasms

**ANAL CANAL****Squamous Cell Carcinoma (SCC) of Anal Canal (above dentate line)**

- most common tumour of anal canal (75%)
- anus prone to human papilloma virus (HPV) infection, therefore at risk for anal squamous intraepithelial lesions (ASIL)
  - high grade squamous intraepithelial lesion (HSIL) and low grade squamous intraepithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5-yr survival

**Malignant Melanoma of Anal Canal**

- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- treatment: wide excision or APR ± chemoradiation
- prognosis: <5% 5-yr survival

**ANAL MARGIN**

- clinical features and treatment as for skin tumours elsewhere
- squamous and basal cell carcinoma, Bowen's disease (SCC in situ) and Paget's disease

## Liver

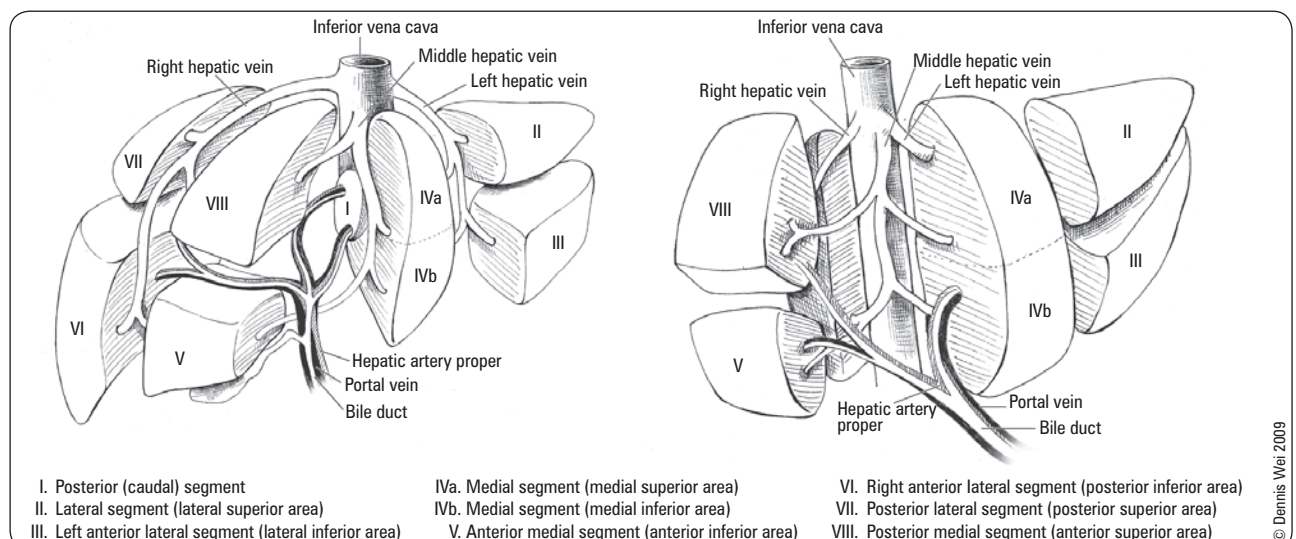


Figure 26. Anatomy of liver

## Liver Cysts

### SIMPLE CYSTS

- most common type of liver cyst, may have multiple simple cysts
- clinical features: usually asymptomatic, if large may present with pain or mass; diagnose with U/S
- treatment: generally not required for simple cysts unless very large
- complications: intracystic hemorrhage (may be confused with complex cysts)

### POLYCYSTIC LIVER DISEASE

- progressive condition where cysts replace much of the liver
- 50% associated with polycystic kidney disease
- treatment: if symptomatic treat by partial liver resection or by creating drainage for cysts

### CHOLEDOCHAL CYSTS

- congenital malformations of pancreaticobiliary tree; majority present before age 10 yr
- 5 types, most extreme form called Caroli's disease (multiple cystic dilations in intrahepatic ducts)
- clinical features: recurrent abdominal pain, intermittent jaundice, RUQ mass, cholangitis, pancreatitis
- diagnosis: U/S, CT, transhepatic cholangiography, LFTs
- treatment:
  - high risk of malignancy, current treatment is complete excision of cysts
  - abnormal pancreaticobiliary junction is associated with increased risk of malignancy
  - liver transplant indicated if cyst involves intrahepatic bile ducts (Caroli's disease)
- complications of choledochal cysts: biliary cirrhosis, portal hypertension, rupture, cholangiocarcinoma

### HYDATID LIVER CYSTS (CYSTIC ECHINOCOCCOSIS)

- etiology:
  - infection with parasite *Echinococcus granulosus* commonly found in Southern Europe, Middle East, Australasia, South America
  - associated with exposure to dogs, sheep and cattle
- clinical features:
  - asymptomatic mass (most often) or chronic pain, hepatomegaly; if large may compress inferior vena cava
  - rupture can cause biliary colic, jaundice, cholangitis, pancreatitis, or anaphylactic reaction
- investigations:
  - detection of anti-*Echinococcus* Ab (IgG) using ELISA
  - U/S, CT: presence of mass, often calcified
  - needle biopsy
- treatment:
  - medical: albendazole (anti-helminthic) – cure up to 30%
  - surgical (risk of spillage into abdomen):
    - ♦ conservative: open endocystectomy or PAIR (Percutaneous Aspiration, Injection of protoscolicidal agent, Re-aspiration)
    - ♦ radical: partial hepatectomy or total pericystectomy

### CYSTADENOMA (PREMALIGNANT)/CYSTADENOCARCINOMA

- clinical features:
  - appear as complex cysts on imaging: internal septae, papillary projections, irregular lining
- all complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk

## Liver Abscesses

### Etiology

- types:
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *E. coli*, *Klebsiella*, *Proteus*, *Strep. milleri*
  - parasitic (amoebic): *Entamoeba histolytica*
  - fungal: *Candida*
- sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

### Clinical Features

- fever, malaise, chills, anorexia, weight loss, abdominal pain, nausea
- RUQ tenderness, hepatomegaly, jaundice

### Investigations

- leukocytosis, anemia, elevated liver enzymes, hemagglutination titres for *Entamoeba* antibodies
- U/S, CXR (right basilar atelectasis/effusion), CT, cyst aspiration with C&S

### Treatment

- treat underlying cause
- generally will treat initially with antibiotics alone and add surgical or percutaneous drainage and IV antibiotics for larger abscesses (initially ceftriaxone + metronidazole or piperacillin/tazobactam)

### Prognosis

- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition

## Neoplasms

### BENIGN LIVER NEOPLASMS

#### Hemangioma (cavernous)

- pathogenesis: most common benign hepatic tumour; results from malformation of angioblastic fetal tissue
- risk factors: F:M = 3:1, steroid therapy, estrogen (exogenous, pregnancy)
- clinical features:
  - usually small and asymptomatic, larger tumours may produce pain or compress nearby structures
  - shock if ruptured (very rare), consumptive coagulopathy if giant (in children)
- investigations:
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement and delayed venous emptying), U/S (homogenous hyperechoic mass), arteriography (rarely used; "cotton wool" appearance), RBC scan
  - biopsy may result in hemorrhage
- treatment:
  - usually none unless tumour bleeds or is symptomatic, then excision by lobectomy or enucleation

#### Focal Nodular Hyperplasia

- pathogenesis: unclear, may be regenerative response to hyperperfusion from anomalous arteries at centre of nodule
- risk factors: female, age 20-50
- clinical features: asymptomatic, rarely grows or bleeds, no malignant potential
- investigations: central stellate scar on CT scan; technetium-99 scan is helpful
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential) → often resected

#### Adenoma

- definition: benign glandular epithelial tumour
- risk factors: female, age 20-50, estrogen (OCP, pregnancy)
- clinical features: asymptomatic, 25% present with RUQ pain or mass
- investigations: CT (well-demarcated masses, often heterogeneous, isodense on non-contrast CT, peripheral enhancement/isodense/hypodense on contrast CT), U/S, biopsy (tendency to bleed following biopsy)
- treatment:
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to hepatocellular carcinoma and spontaneous rupture/hemorrhage
  - smaller lesions can be effectively treated with embolization

### MALIGNANT LIVER NEOPLASMS

#### Primary

- usually hepatocellular carcinoma (HCC)/hepatoma
- others include angiosarcoma, hepatoblastoma, hemangioendothelioma
- epidemiology: 3rd leading cause of cancer death worldwide, 9th in United States; highest in Africa, China, Taiwan
- risk factors:
  - chronic liver inflammation: chronic hepatitis B (inherently oncogenic) and C, cirrhosis (especially macronodular), hemochromatosis,  $\alpha_1$ -anti-trypsin deficiency
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, Betel nuts
  - chemical carcinogens (aflatoxin, microcystin, vinyl chloride – associated with angiosarcoma)
- clinical features:
  - RUQ discomfort, right shoulder pain
  - jaundice, weakness, weight loss,  $\pm$  fever (if central tumour necrosis)
  - hepatomegaly, bruit, hepatic friction rub



Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrahepatic cancers. They commonly arise from breast, lung and colorectal cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure.

- ascites with blood (sudden intra-abdominal hemorrhage)
- paraneoplastic syndromes – hypoglycemia, hypercalcemia, erythrocytosis, watery diarrhea
- metastasis: lung, bone, brain, peritoneal seeding
- investigations:
  - elevated ALP, bilirubin, and  $\alpha$ -fetoprotein (80% of patients)
  - U/S (poorly-defined margins with internal echos), triphasic CT (enhancement on arterial phase and washout on portal venous phase), MRI, CT or MRI angiography
  - biopsy
- treatment:
  - cirrhosis is a *relative* contraindication to tumour resection due to decreased hepatic reserve
  - surgical: resection (10% of patients have resectable tumours)
  - liver transplant; may use bridging therapy while awaiting transplant
    - absolute contraindications:** extrahepatic disease, vascular invasion
    - relative contraindications:** dependent on liver transplant protocol based on staging criteria followed by transplant centre
  - non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), chemotherapy (consider sorafenib for HCC; pre-op chemotherapy for hepatoblastoma is standard of care), radiotherapy
- prognosis:
  - median survival: 6-20 mo
  - 5-yr survival: all patients – 5%; patients undergoing complete resection – 11-40%

### Secondary

- most common hepatic malignancy
- etiology:
  - GI (colorectal most common), lung, breast, pancreas, ovary, uterus, kidney, gallbladder, prostate
- treatment:
  - hepatic resection for metastatic colorectal liver metastases if control of primary is possible, no extrahepatic or extrapulmonary metastases and if possibility of “curative” resection
  - possible chemotherapy
- prognosis: 30-40% 5-yr survival with a “curative” resection; prognosis same if metastases are multilobar compared with confined to one lobe



### Staging Criteria for Hepatocellular Carcinoma

<b>Milan Criteria*</b>	1 tumour $\leq 5$ cm Up to 3 tumours each $\leq 3$ cm
<b>UCSF Criteria*</b>	1 tumour $\leq 6.5$ cm Up to 3 tumours each $\leq 4.5$ cm, total diameter $\leq 8$ cm
<b>Toronto Criteria*</b>	No tumour size or number restrictions No systemic symptoms Not poorly differentiated

\*Each criteria assumes no extrahepatic and no macrovascular invasion.



### Differential Diagnosis of Metastatic Liver Mass

Some GU Cancers Produce Bumpy Lumps:

Stomach  
GenitoUrinary cancers  
(kidney, ovary, uterus)  
Colon  
Pancreas  
Breast  
Lung



### Child-Turcotte-Pugh Score (Prognosis of Chronic Liver Disease/Cirrhosis, Including Postoperatively)

	1 Point	2 Points	3 Points
Albumin (g/L)	$>35$	28-35	$<28$
Ascites	Absent	Easily controlled	Poorly controlled
Bilirubin (umol/L)	$<34$	34-51	$>51$
(mg/dL)	$<2.0$	2.0-3.0	$>3.0$
Coagulation (INR)	$<1.7$	1.7-2.3	$>2.3$
Hepatic encephalopathy	None	Minimal (Grade I-II)	Advanced (Grade III-IV)
Points	Class	One Year Survival	Two Year Survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%



### Living Liver Donors vs. Deceased Liver Donors

The right lobe of a living donor liver is transplanted into the recipient whereas whole livers from deceased donors are transplanted orthotopically into the recipient.

## Liver Transplantation

Table 18. Conditions Leading to Transplantation

Parenchymal Disease	Cholestatic Disease	Inborn Errors	Tumours
Chronic hepatitis B or C*	Biliary atresia**	$\alpha_1$ -anti-trypsin deficiency	Hepatocellular carcinoma
Alcoholic cirrhosis	Primary biliary cirrhosis	Wilson's disease	
Acute liver failure	Sclerosing cholangitis	Hemochromatosis	
Budd-Chiari syndrome			
Congenital hepatic fibrosis			
Cystic fibrosis (CF)			
Autoimmune Hepatitis			
Cryptogenic Cirrhosis			
Wilson's disease			

\*Leading cause in adults; \*\*leading cause in children

### Clinical Indications

- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially decompensated cirrhosis, unresectable primary liver cancers and fulminant hepatic failure
- end-stage liver disease with life expectancy  $<1$  yr and if no other therapy is appropriate
- progressive jaundice, refractory ascites, spontaneous hepatic encephalopathy, recurrent sepsis, fulminant hepatic failure
- recurrent variceal hemorrhage, coagulopathy, severe fatigue

### Criteria for Transplantation

- Model for End-Stage Liver Disease (MELD): considers probability of death within 3 mo if patient does not receive transplant; based on creatinine, bilirubin, INR; MELD scores from 6-40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: patient must have  $\geq 7$  points (Class B)

### Contraindications

- active alcohol/substance abuse
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease



## Post-op Complications

- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: hypertension, renal disease, diabetes, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

## Prognosis

- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

# Biliary Tract

## Cholelithiasis

### Definition

- the formation of gallstones

### Pathogenesis

- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excessive hepatic cholesterol secretion → bile salts and lecithin are "overloaded" → supersaturated cholesterol can precipitate and form gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

### Risk Factors

- cholesterol stones:
  - obesity, age <50
  - estrogens: female, multiparity, OCPs
  - ethnicity: First Nations heritage (especially Pima Indians) > Caucasian > Black
  - terminal ileal resection or disease (e.g. Crohn's disease)
  - impaired gallbladder emptying: starvation, TPN, DM
  - rapid weight loss: rapid cholesterol mobilization and biliary stasis
- pigment stones (contain calcium bilirubinate):
  - cirrhosis
  - chronic hemolysis
  - biliary stasis (strictures, dilation, biliary infection)
- protective factors: statins, vitamin C, coffee

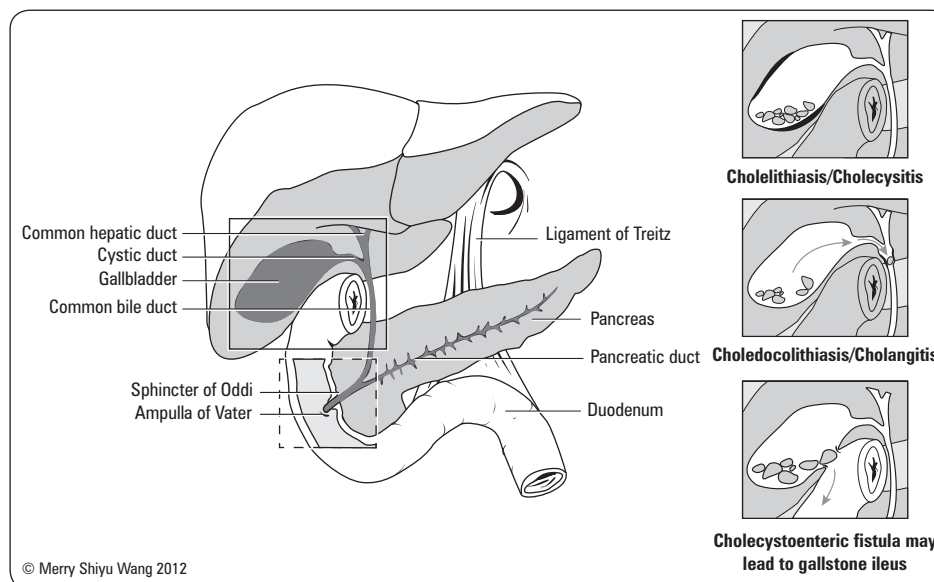


Figure 27. Gallstone disease

### Clinical Features

- asymptomatic (80%):
  - most do NOT require treatment
  - consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli's disease, porcelain or calcified gallbladder), sickle cell disease, pediatric patient, bariatric surgery, diabetes, immunosuppression



### Which Matters Most: Number of Tumors, Size of the Largest Tumour, or Total Tumour Volume?

*Liver Transplant 2011;17:S58-66*

**Purpose:** To determine if the size and/or number of hepatocellular carcinoma (HCC) nodules predict disease recurrence and survival after liver transplantation.

**Methods:** Systematic review and meta-analysis.

**Results:** 74 studies were included for analysis. Patients beyond the Milan criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the UCSF criteria had reduced overall and disease-free survivals and higher recurrence. Patients outside the Milan criteria but within the UCSF criteria had reduced overall and disease-free survivals. Overall and disease-free survivals were reduced for patients with larger total tumour diameter,  $\geq 10$  cm vs.  $< 10$  cm and  $\geq 9$  cm vs.  $< 9$  cm, respectively. Similarly, patients with higher diameter of largest tumour nodule ( $\geq 3$  cm vs.  $< 3$  cm) had reduced overall survival and higher recurrence. Overall and disease-free survivals were reduced and recurrence higher for patients with tumour size  $\geq 5$  cm vs.  $< 5$  cm. Mixed results were found regarding number of tumour nodules.

**Conclusion:** Tumour size and volume are important factors in survival after liver transplantation.



### Living Donor Liver Transplantation Versus Deceased Donor Liver Transplantation for Hepatocellular Carcinoma: Comparable Survival and Recurrence

*Liver Transplant 2012;18:315-322*

**Purpose:** To compare the overall survival and hepatocellular carcinoma (HCC) recurrence rates after living donor liver transplantation (LDLT) versus deceased donor liver transplantation (DDLT) in a series of patients with HCC.

**Methods:** Study conducted between 1996 and 2009 at a single centre. 345 patients with HCC undergoing liver transplantation included.

**Results:** The overall survival rates at 1, 3, and 5 yr did not significantly differ between the LDLT and DDLT groups ( $p = 0.62$ ). Disease free survival at 1, 3, and 5 yr did not differ between the groups ( $p = 0.82$ ). The recurrence rates at 1, 3, and 5 yr also did not differ between the two groups ( $p = 0.54$ ).

**Conclusion:** LDLT and DDLT lead to similar survival and recurrence rates.



### Summary of Biliary Tract Conditions

Gall Bladder	Asymptomatic	Pain Only	Infection + Pain
Cholelithiasis	✓ (majority)		
Biliary Colic		✓	
Cholecystitis			✓
Common Bile Duct	Asymptomatic	Pain Only	Infection + Pain
Choledocholithiasis	✓ (majority)	✓	
Cholangitis			✓ (majority)



### Risk Factors for Cholesterol Stones

4Fs  
Fat  
Female  
Fertile  
Forties

- biliary colic (10-25%)
- cholecystitis
- choledocholithiasis (8-15%)
- cholangitis
- gallstone pancreatitis (see *Acute Pancreatitis*, GS50)
- gallstone ileus

### Investigations

- U/S – diagnostic procedure of choice:
  - image for signs of inflammation, obstruction, localization of stones
- ERCP (endoscopic retrograde cholangiopancreatography):
  - visualization of upper GI tract, ampullary region, biliary and pancreatic ducts
  - method for treatment of CBD stones in periampullary region
  - complications: traumatic pancreatitis (1-2%), pancreatic or biliary sepsis
- MRCP (magnetic resonance cholangiopancreatography):
  - same information gained as ERCP but non-invasive
  - cannot be used for therapeutic purposes
- PTC (percutaneous transhepatic cholangiography):
  - injection of contrast via needle passed through hepatic parenchyma
  - useful for proximal bile duct lesions or when ERCP fails or not available
  - requires prophylactic antibiotics
  - contraindications: coagulopathy, ascites, peri/intrahepatic sepsis, disease of right lower lung or pleura
  - complications: bile peritonitis, chylothorax, pneumothorax, sepsis, hemobilia
- HIDA scan (hepatobiliary imino-diacetic acid scan):
  - used less commonly
  - radioisotope technetium-99 injected into a vein is excreted in high concentrations into bile, allowing visualization of the biliary tree
  - does not visualize stones; diagnosis by seeing occluded cystic duct or CBD

## Biliary Colic

### Pathogenesis

- gallstone transiently impacted in cystic duct, no infection

### Clinical Features

- steady, severe dull pain in epigastrium or RUQ for minutes to hours, crescendo-decrescendo pattern
- may present with chest pain
- frequently occurs at night or after fatty meal, not after fasting
- can radiate to right shoulder or scapula
- patients often restless
- no peritoneal findings, no systemic signs

### Investigations

- normal blood work: CBC, electrolytes, LFTs, bilirubin, amylase
- U/S shows cholelithiasis, may show stone in cystic duct

### Treatment

- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success):
  - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, vessel injury
  - laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery
  - risk of open cholecystectomy higher in emergency situations

## Acute Cholecystitis



### Pathogenesis

- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see *Acalculous Cholecystitis*, GS47)

### Clinical Features

- often have history of biliary colic
- severe constant (hours to days) epigastric or RUQ pain, anorexia, nausea, vomiting, low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable, tender gallbladder (in 33%)
- Boas' sign: right subscapular pain

### Investigation

- bloodwork: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT and ALP
- U/S: 98% sensitive, consider HIDA scan if U/S negative



### 2 Most Important Lab Tests for Biliary Pain:

- Amylase
- Bilirubin



Biliary colic is a **constant** pain not colicky.



### Early versus Delayed Laparoscopic Cholecystectomy for Biliary Colic

*Cochrane DB Syst Rev 2008;4:CD007196*

**Study:** To assess the benefits and harms of early versus delayed laparoscopic cholecystectomy for patients with biliary colic due to gallstones.

**Selection criteria:** Only RCTs. 1 study including 75 patients found.

**Results:** During the waiting period in the delayed group (mean 4.2 mo), the complications that the patients suffered included severe acute pancreatitis resulting in mortality (1), empyema of gallbladder (1), gallbladder perforation (1), acute cholecystitis (2), cholangitis (2), obstructive jaundice (2), and recurrent biliary colic requiring hospital visits (5). The rate of conversion to open cholecystectomy was lower in the early group (0%) than the delayed group (20%). There was a statistically significant shorter operating time and hospital stay in the early group than the delayed group (WMD -14.80 min, 95% CI -18.02 to -11.58 and -1.25 d, 95% CI -2.05 to -0.45 respectively). Fourteen patients (35%) required 18 hospital admissions for symptoms related to gallstones during the mean waiting period of 4.2 mo in the delayed group.

**Conclusion:** Early laparoscopic cholecystectomy (<24 h of diagnosis of biliary colic) decreases the morbidity during the waiting period for elective laparoscopic cholecystectomy, decreases the rate of conversion to open cholecystectomy, decreases operating time, and decreases hospital stay.



### Acalculous Cholecystitis

- Acute or chronic cholecystitis in the absence of stones, typically due to gallbladder ischemia, stasis
- Risk factors: DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis
- Clinical features same as Acute cholecystitis, occurs in 20% of cases of acute cholecystitis
- Investigations: U/S shows sludge in gallbladder, other U/S features of cholecystitis (see above), CT or HIDA scan
- Treatment: broad-spectrum antibiotics, cholecystectomy, if patient unstable → cholecystostomy



### Rouviere's Sulcus

Fissure between right lobe and caudate process of liver. Keeping dissection anterior to this landmark prevents bile duct injury.



### Critical View of Safety

Space between the gallbladder and liver clear of any structures other than the cystic artery.

## Complications

- gallbladder mucocele (hydrops): long term cystic duct obstruction results in mucous accumulation in gallbladder (clear fluid)
- gangrene (20%), perforation (2%): result in abscess formation or peritonitis
- empyema of gallbladder: suppurative cholecystitis, pus in gallbladder + sick patient
- cholecystoenteric fistula, from repeated attacks of cholecystitis, can lead to gallstone ileus
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall or pericholecystic space (risk in diabetic patient)
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct

## Treatment

- admit, hydrate, NPO, NG tube (if persistent vomiting from associated ileus), analgesics once diagnosis is made
- antibiotics:
  - cefazolin if uncomplicated cholecystitis
- cholecystectomy:
  - early (within 72 h) vs. delayed (after 6 wk)
    - equal morbidity and mortality
    - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
    - emergent OR indicated if high risk, e.g. emphysematous
  - laparoscopic is standard of care (convert to open for complications or difficult case)
    - laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-op pain, increased risk of bile duct injury
- intra-operative cholangiography (IOC):
  - indications: clarify bile duct anatomy, obstructive jaundice, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct ( $>15$  mm), single faceted stone in gallbladder, bilirubin  $>137$   $\mu\text{mol/L}$
- percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated



### Mirizzi Syndrome

Extrinsic compression of the common hepatic duct by a gallstone in the cystic duct or Hartmann's pouch. Impacted gallstone may erode into the CHD or CBD, creating a cholecystohepatic or cholecystocholedocal fistula. Mirizzi syndrome has an association with gallbladder cancer.



**Biliary colic** is treated with analgesia and elective cholecystectomy

**Acute cholecystitis** is treated with antibiotics and early cholecystectomy



### Does this Patient have Acute Cholecystitis?

JAMA 2003;289:80-86

**Purpose:** To determine which patients need imaging techniques to diagnose acute cholecystitis.

**Methods:** 17 studies published between 1950 and 2002 were included. They evaluated the findings of history, physical exam, and basic laboratory tests in adult patients with abdominal pain or suspected acute cholecystitis. Studies used a control group with no diagnosis of acute cholecystitis, and acute cholecystitis was diagnosed through various methods including surgery and pathologic examination.

**Results:** No clinical or laboratory finding was statistically significant to rule in or rule out the diagnosis of acute cholecystitis. However, a positive Murphy's sign ( $\text{LR+} = 2.8$ , 95% CI 0.8-86), and absence of right upper quadrant tenderness ( $\text{LR-} 0.4$ , 95% CI 0.2-1.1) were the most consistent in their diagnostic value, despite neither being statistically significant.

**Conclusions:** No single clinical findings or laboratory test can rule in or rule out the diagnosis of acute cholecystitis. It is through a combination of clinical findings and diagnostic imaging that the diagnosis of acute cholecystitis is made in patients presenting with abdominal pain.



### Laparoscopic vs. Open Cholecystectomy

#### Laparoscopic Cholecystectomy

- Shorter operating time
- Shorter length of stay
- Shorter sick leave
- Shorter time to return to daily activities
- Less postoperative pain
- Decreased use of postoperative analgesia
- Decreased reduction in pulmonary function\*
- Fewer pulmonary complications
- Decreased acute phase response
- Less impairment in intestinal motility\*

#### Open Cholecystectomy

- Lower conversion rates to open surgery (for mini-laparotomies)

\*NOTE:

Pulmonary function =  $\text{O}_2$  consumption, spirometric parameters, arterial blood gases, and acid-base balance  
Intestinal motility = auscultating intestinal peristalsis, abdominal circumference measurement, and time interval to restitution of defecation

## Acalculous Cholecystitis

### Definition

- acute or chronic cholecystitis in the absence of stones

### Pathogenesis

- typically due to gallbladder ischemia, stasis

### Risk Factors

- DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis

### Clinical Features

- see *Acute Cholecystitis*, GS46
- occurs in 20% of cases of acute cholecystitis

### Investigations

- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see *Acute Cholecystitis*, GS46)
- CT or HIDA scan

### Treatment

- broad-spectrum antibiotics, cholecystectomy
- if patient unstable  $\rightarrow$  cholecystostomy

## Choledocholithiasis

### Definition

- stones in common bile duct (CBD)

### Clinical Features

- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, fluctuating jaundice
- primary vs. secondary stones:
  - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, cystic fibrosis)
  - secondary: formed in gallbladder (85% of cases in U.S.)

### Investigations

- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GGT later
- amylase/lipase: to rule out gallstone pancreatitis
- U/S: intra/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
- ERCP, PTC
- MRCP (90% sensitive, almost 100% specific, not therapeutic)

### Complications

- cholangitis, pancreatitis, biliary stricture and biliary cirrhosis

### Treatment

- if no evidence of cholangitis: treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients



#### American Society of Gastrointestinal Endoscopy 2010 Predictors for Risk of CBD Stones:

- Very strong:
  - CBD stone on ultrasound
  - Clinical ascending cholangitis
  - Bilirubin > 68  $\mu\text{mol/L}$
- Strong:
  - CBD dilated > 6 mm on ultrasound
  - Bilirubin 31-68  $\mu\text{mol/L}$
- Moderate:
  - Abnormal liver test (besides bilirubin)
  - Age > 55 yr
  - Clinical gallstone pancreatitis

## Acute Cholangitis

### Pathogenesis

- obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration and biliary sepsis – may be life-threatening, especially in elderly

### Etiology

- choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), biliary stent
- organisms: *E. coli*, *Klebsiella*, *Pseudomonas*, *Enterococcus*, *B. fragilis*, *Proteus*

### Clinical Features

- Charcot's triad: fever, RUQ pain, jaundice
- Reynold's pentad: fever, RUQ pain, jaundice, shock, confusion
- may have nausea, vomiting, abdominal distention, ileus, acholic stools, tea-coloured urine (elevated direct bilirubin)



#### Charcot's Triad

Fever, RUQ pain, jaundice.



#### Reynolds' Pentad

Fever, RUQ pain, jaundice, shock, confusion.

### Investigations

- CBC: elevated WBC + left shift
- may have positive blood cultures
- LFTs: obstructive picture (elevated ALP, GGT and conjugated bilirubin, mild increase in AST, ALT)
- amylase/lipase: rule out pancreatitis
- U/S: intra/extra-hepatic duct dilatation

### Treatment

- initial: NPO, fluid and electrolyte resuscitation,  $\pm$  NG tube, IV antibiotics (treats 80%)
- decompression:
  - ERCP + sphincterotomy: diagnostic and therapeutic
  - PTC with catheter drainage: if ERCP not available or unsuccessful
  - laparotomy with CBD exploration and T-tube placement if above fails
- all patients should also have a cholecystectomy, unless contraindicated

### Prognosis

- suppurative cholangitis mortality rate: 50%



#### Common Bacteria in Biliary Tract

##### KEEPS

*Klebsiella*  
*Enterococcus*  
*E. Coli*, *Enterobacter*  
*Proteus*, *Pseudomonas*  
*Serratia*

## Gallstone Ileus

### Pathogenesis

- repeated inflammation causing a cholecystoenteric fistula (usually duodenal)  $\rightarrow$  large gallstone enters the gut and impacts at or near the ileocecal valve, causing a true bowel obstruction (note: ileus is a misnomer in this context)

### Clinical Features

- crampy abdominal pain, nausea, vomiting (see *Bowel Obstruction*, GS24)

### Investigations

- AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, air in biliary tree (pneumobilia) (40%)
- CT: biliary tract air, obstruction, gallstone in intestine
- Rigler's triad: pneumobilia (air in biliary tree), small bowel obstruction (partial or complete), gallstone (usually in right iliac fossa)



#### Bouveret's Syndrome

Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula.



#### Rigler's Triad of Gallstone Ileus:

- Pneumobilia
- Small bowel obstruction
- Gallstone

**Treatment**

- fluid resuscitation, NG decompression
- surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- may close fistula surgically or manage expectantly (can resolve spontaneously)
- cholecystectomy either during enterolithotomy or after recovery if patient experiences gallbladder symptoms

## Carcinoma of the Gallbladder

**Risk Factors**

- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (*Salmonella*, *Helicobacter*), abnormal pancreaticobiliary duct junction

**Clinical Features**

- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of elective cholecystectomies)
- many patients are asymptomatic until late
- local: vague RUQ pain,  $\pm$  palpable RUQ mass
- Courvoisier's gallbladder: an enlarged, often palpable gallbladder in a patient with carcinoma of the head of the pancreas; associated with jaundice due to obstruction of the common bile duct
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- early local extension to liver, may extend to stomach, duodenum
- early metastasis common to liver, lung, bone

**Investigations**

- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, good for staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

**Treatment**

- if carcinoma of the gallbladder is suspected preoperatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, dissection of hepatoduodenal lymph nodes

**Prognosis**

- poor 5 yr survival (10%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

## Cholangiocarcinoma

**Definition**

- malignancy of extra- or intrahepatic bile ducts

**Risk Factors**

- age 50-70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, *Clonorchis sinensis* infection (liver fluke), chronic intrahepatic stones (hepatolithiasis)

**Clinical Features**

- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, pale stools
- anorexia, weight loss, RUQ pain, Courvoisier's sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery
- Klatskin tumour: cholangiocarcinoma located at bifurcation of common hepatic duct

**Investigations**

- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup



Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma.

**Courvoisier's Sign**

Palpable, nontender distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger.



## Treatment

- generally palliative
- if resectable: biliary drainage and wide excision margin
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)

## Prognosis

- radiotherapy useful for additional palliation, chemotherapy may be helpful
- the more proximal to the liver, the worse the prognosis
- overall 5-yr survival: 15%



### Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centers

*Gastroenterology* 2012;143:88-98

**Purpose:** To determine the effectiveness of neoadjuvant chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma and to determine the appropriateness of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) criteria for model of end-stage liver disease (MELD) exception for patients with this disease.

**Methods:** Study conducted from 1993-2010 in 12 transplant centers. 287 patients included.

**Results:** Median follow-up was 2.5 yr. 43% of patients (n = 122) died after a median of 1.2 yr from presentation, and of these, 60 died pretransplant. Post-transplant, 43 patients had recurrences and 62 died. Recurrence-free survival at 2, 5, and 10 yr were 78%, 65%, and 59%, respectively. Intention-to-treat survival rates at 2 and 5 yr were 68% and 53%, respectively. 25% of patients left the waiting list after a median of 4.6 mo. The waiting list drop-out rate increased by an average of 11.5% every 3 mo. Patients who received transplantation outside of the criteria for MELD exception or who had a malignancy within 5 yr had significantly worse recurrence-free survival compared to those who met the criteria (HR = 2.98, 95% CI: 1.79, 4.95). Recurrence-free survival at 5 yr was shorter for patients with tumors >3 cm versus ≤3 cm (p < 0.001).

**Conclusions:** Neoadjuvant chemoradiation and liver transplantation are effective treatments for unresectable perihilar cholangiocarcinoma. Furthermore, the UNOS/OPTN criteria for MELD exception appear to be appropriate.



### Ranson's Criteria

#### A. At admission

1. Age > 55 yr
2. WBC > 16 × 10<sup>9</sup>/L
3. Glucose > 11 mmol/L
4. LDH ≥ 350 IU/L
5. AST > 250 IU/L

#### B. During initial 48 h

1. Hct drop > 10%
2. BUN rise > 1.8 mmol/L
3. Arterial PO<sub>2</sub> < 60 mmHg
4. Base deficit > 4 mmol/L
5. Calcium < 2 mmol/L
6. Fluid sequestration > 6 L

#### C. Interpretation

- ≥ 2 = difficult course
- ≥ 3 = high mortality (≥ 15%)

# Pancreas

## Acute Pancreatitis



- see [Gastroenterology](#), G44

### GALLSTONE PANCREATITIS (35% of acute pancreatitis)

#### Pathogenesis

- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

#### Clinical Features (pancreatitis of any etiology)

- pain (epigastric pain radiating to back), nausea, vomiting, ileus, peritoneal signs, jaundice, fever
- Ingelfinger's sign: pain worse when supine, better when sitting forward
- rarely may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)

#### Investigations

- high amylase (higher than alcoholic pancreatitis), lipase, leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), edematous pancreas
- CXR, AXR, CT (if severe to evaluate for complications)

#### Treatment

- supportive
- enteral nutrition
- NPO, hydration, analgesia and antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if failure of conservative management (benefits of early ERCP controversial)
- early ERCP if concomitant cholangitis
- **surgical indications** in acute pancreatitis (rare):
  - debridement and drain placement for necrotizing pancreatitis if refractory to medical management, if septic or in ICU without other sources of sepsis

#### Complications

- pseudocyst (collection of pancreatic secretions >4 wk old surrounded by a defined wall of granulation tissue)
- abscess/infection, necrosis
- splenic/mesenteric/portal vessel thrombosis or rupture
- pancreatic ascites/pancreatic pleural effusion
- diabetes
- ARDS/sepsis/multiorgan failure
- coagulopathy/DIC
- encephalopathy
- severe hypocalcemia



## Chronic Pancreatitis

- see also [Gastroenterology](#), G46

### Surgical Treatment

- treatment is generally medical
- indications for surgery:
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, rupture
  - CBD obstruction (e.g. strictures), duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- pre-op CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options:
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery
- surgical options:
  - drainage procedures: only effective if ductal system is dilated
    - ♦ Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
  - pancreatectomy: best option in absence of dilated duct
    - ♦ proximal disease: Whipple procedure (pancreaticoduodenectomy) – pain relief in 80%
    - ♦ distal disease: distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy
    - ♦ total pancreatectomy: refractory disease
  - denervation of celiac ganglion and splanchnic nerves
- pseudocyst (often resolve spontaneously with pancreatic rest):
  - cyst wall must be mature prior to drainage (4-6 wk)
  - pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first
  - percutaneous catheter drainage
  - surgical drainage (gold standard):
    - ♦ cystgastrostomy
    - ♦ cystenterostomy
    - ♦ resection
  - endoscopic drainage:
    - ♦ cystgastrostomy
    - ♦ cystduodenostomy
  - consider biopsy of cyst wall to rule out cystadenocarcinoma



The hallmark of chronic pancreatitis is epigastric pain radiating to the back.

## Pancreatic Cancer

### Epidemiology

- fourth most common cause of cancer-related mortality in both men and women in Canada
- M:F = 1.3:1, average age: 50-70

### Risk Factors

- increased age
- smoking: 2-5x increased risk, most clearly established risk factor
- high fat/low fibre diets, heavy alcohol use
- obesity
- DM, chronic pancreatitis
- partial gastrectomy, cholecystectomy
- chemicals: betanaphthylamine, benzidine
- African descent

### Clinical Features

- head of the pancreas (70%):
  - weight loss, obstructive jaundice, vague constant mid-epigastric pain (often worse at night, may radiate to back)
  - painless jaundice (occurs more often with peri-ampullary), Courvoisier's sign (see sidebar GS49)
  - palpable tumour mass → generally incurable
- body or tail of pancreas (30%):
  - tends to present later and usually inoperable
  - weight loss, vague mid-epigastric pain
  - <10% jaundiced
  - sudden onset diabetes

### Investigations

- serum chemistry is non-specific, can have elevated ALP and bilirubin >300 µmol/L
- CA 19-9 (most useful serum marker of pancreatic cancer)
- U/S, contrast CT (also evaluates metastasis and resectability), ERCP, MRI, MRCP



Vague abdominal pain with weight loss ± jaundice in a patient over 50 yr old is pancreatic cancer until proven otherwise.



**Trousseau's Sign**  
Spontaneous peripheral venous thrombosis, often associated with pancreatic and other cancers.

## Pathology

- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: mucinous cystic neoplasm (MCN), acinar cell carcinoma, islet-cell (insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma)
- see *Surgical Endocrinology*, GS60 for insulinoma

## Treatment

- resectable (20% of pancreatic cancer)
  - no involvement of liver, peritoneum or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure – 5% mortality
  - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
- borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
- non-resectable (palliative → relieve pain, obstruction)
  - most body/tail tumours are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
  - chemotherapy (gemcitabine, folfirinix), radiotherapy – only slightly increase survival

## Prognosis

- most important prognostic indicators are lymph node status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5-yr survival is 1%
- 20% 5-yr survival following resection
- median survival for unresectable disease: 8-12 mo if locally advanced, 3-6 mo if metastatic

**Table 19. TNM Classification System for Exocrine and Endocrine Tumours of the Pancreas**

Primary Tumour (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
TX Primary tumour cannot be assessed	NX Regional lymph nodes cannot be assessed	M0 No distant metastasis
T0 No evidence of primary tumour	N0 No regional lymph node metastasis	M1 Distant metastasis
Tis Carcinoma in situ	N1 Regional lymph node metastasis	
T1 Tumour limited to pancreas, <2 cm in greatest dimension		
T2 Tumour limited to pancreas, >2 cm in greatest dimension		
T3 Tumour extends beyond pancreas, no involvement of celiac axis or superior mesenteric artery		
T4 Tumour involves celiac axis or superior mesenteric artery (unresectable)		

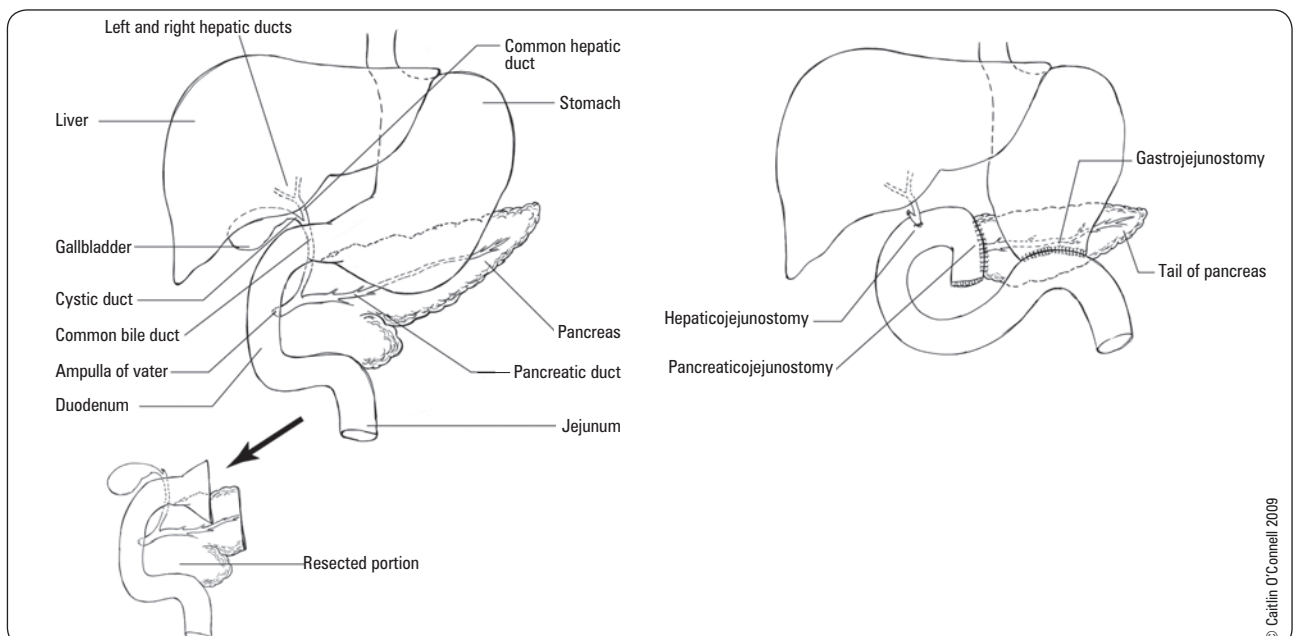


### Steps of a Whipple Resection (Pancreaticoduodenectomy):

1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the duodenum and head of the pancreas with identification of the superior mesenteric vein
3. Mobilization of the stomach and proximal duodenum, transection of the stomach or proximal duodenum
4. Dissection of the hepatoduodenal ligament with skeletonization of the porta hepatis
5. Cholecystectomy and division of the bile duct
6. Mobilization and division of the proximal jejunum
7. Transection of the pancreatic neck and division of any remaining attachments
8. Reconstruction of gastrointestinal continuity: pancreaticojejunostomy, hepaticojejunostomy, gastro(duodeno)jejunostomy

### Removed:

- Common bile duct
- Gallbladder
- Duodenum
- Pancreatic head
- Distal stomach (sometimes)



**Figure 28. Schematic of Whipple resection, showing the resected components**

# Spleen

## Splenic Trauma

- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr's sign

### Treatment

- non-operative:
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative:
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
  - partial splenectomy, rarely performed due to risk of recurrent hemorrhage
  - total splenectomy if patient unstable or high-grade injury



#### Kehr's Sign

Left shoulder pain due to diaphragmatic irritation from splenic rupture, worsens with inspiration.

## Splenectomy

### Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenia purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenia purpura (TTP), sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIg

### Complications

- short-term:
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas)
  - post-op thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term:
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk in those <16 yr old)
    - ♦ 50% mortality
    - ♦ prophylaxis with vaccinations, ideally 2 wk pre- or post-op (*pneumococcal*, *H. influenzae* and *meningococcus*)
    - ♦ liberal use of penicillin especially in children <6 yr old
  - splenosis: intra-abdominal "seeding" of splenic tissue during removal

## Breast

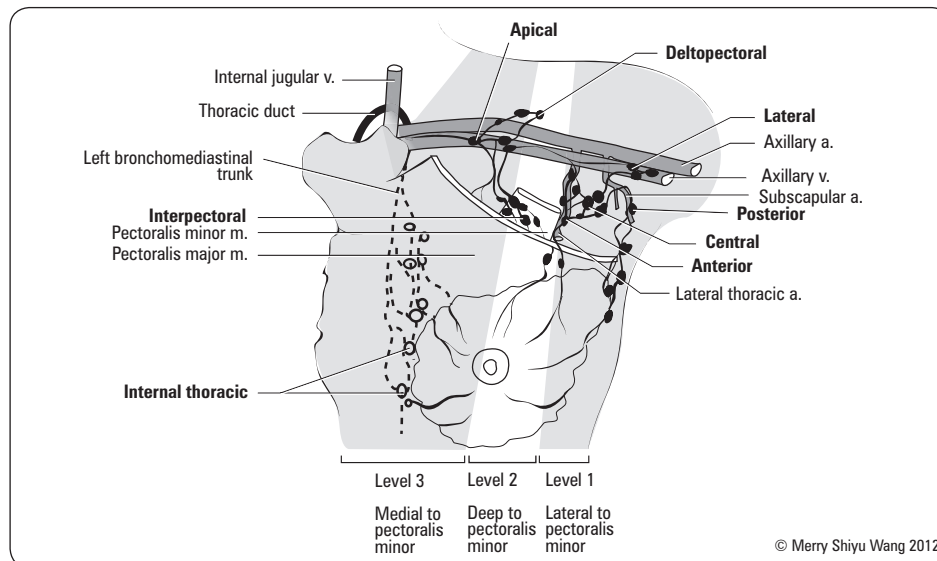


Figure 29. Anatomy of the breast



### Levels of Axillary Lymph Nodes

**Level I:** lateral to pectoralis minor

**Level II:** deep to pectoralis minor

**Level III:** medial to pectoralis minor

(Higher level = worse prognosis)

## Benign Breast Lesions

### NON-PROLIFERATIVE LESIONS

- also known as fibrocystic change, chronic cystic mastitis, mammary dysplasia
- benign breast condition characterized by fibrous and cystic changes in the breast
- no increased risk of breast cancer
- age 30 to menopause (and after if HRT used)
- clinical features:
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, nipple discharge (straw-like, brown or green)
- treatment:
  - evaluation of breast mass and reassurance
  - if >40 yr old: mammography every 3 yr
  - no strong evidence for avoidance of xanthine-containing products (coffee, tea, chocolate, cola)
  - analgesia (ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine



### DDx for Breast Mass

#### Benign:

- Fibrocystic changes
- Fibroepithelial lesions (fibroadenoma most common; benign phyllodes also)
- Fat necrosis
- Papilloma/papillomatosis
- Galactocele
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
- Abscess
- Silicone implant

#### Malignant:

- Breast ca (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)

### PROLIFERATIVE LESIONS – No Atypia

#### Fibroadenoma

- most common benign breast tumour in women under age 30
- risk of subsequent breast cancer is increased only if fibroadenoma is complex, there is adjacent atypia or a strong family history of breast cancer
- clinical features:
  - nodules: smooth, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone dependent
  - unlike cysts, needle aspiration yields no fluid
- investigations:
  - core or excisional biopsy required
  - ultrasound and FNA alone cannot differentiate fibroadenoma from Phyllodes tumour
- treatment:
  - generally conservative: serial observation
  - consider excision if size 2-3 cm and growing on serial ultrasound (q6mo x 2 yr is usual follow-up), if symptomatic or patient preference

#### Intraductal Papilloma

- solitary intraductal benign polyp
- present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge), breast mass, nodule on U/S
- can harbour areas of atypia or DCIS
- treatment: excision of involved duct to ensure no atypia

**Ductal Hyperplasia Without Atypia**

- increased number of cells within the ductal space
- cells retain benign cytology
- no treatment required
- slightly increased cancer risk if moderate or florid hyperplasia

**PROLIFERATIVE LESIONS – With Atypia****Atypical Hyperplasias**

- can involve ducts (ductal hyperplasia with atypia) or lobules (lobular hyperplasia with atypia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

**OTHER LESIONS****Fat Necrosis**

- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction,  $\pm$  tenderness
- regress spontaneously, but complete imaging  $\pm$  biopsy to rule out carcinoma

**Mammary Duct Ectasia**

- obstruction of a subareolar duct leading to duct dilation, inflammation, and fibrosis
- may present with nipple discharge, bluish mass under nipple, local pain
- risk of secondary infection (abscess, mastitis)
- resolves spontaneously

**Montgomery Tubercle**

- Montgomery tubercles (or Morgagni tubercles) are papular projections at the edge of the areola
- obstruction of these glands can lead to inflammation or cystic collections (cyst of Montgomery aka retroareolar cyst)
- if signs of secondary infection, start treatment for mastitis
- resolves spontaneously in weeks to years

**Abscess**

- lactational (see [Obstetrics](#), OB51) vs. periductal/subareolar
- unilateral localized pain, tenderness, erythema, subareolar mass, nipple discharge, nipple inversion
- rule out inflammatory carcinoma, as indicated
- treatment: initially broad-spectrum antibiotics and I&D, if persistent total duct excision (definitive)
- if mass does not resolve: U/S to assess for presence of abscess, core biopsy to exclude cancer, consider MRI



## Breast Cancer

**Epidemiology**

- 2nd leading cause of cancer mortality in women (1st is lung cancer)
- 1/9 of women in Canada will be diagnosed with breast cancer in their lifetime
- 1/27 of women in Canada will die from breast cancer

**Risk Factors**

- gender (99% female)
- age (80% >40 yr old)
- important risk factors are prior history of breast cancer and/or prior breast biopsy (regardless of pathology)
- 1st degree relative with breast cancer (greater risk if relative was premenopausal)
- increased risk with high breast density, nulliparity, first pregnancy >30 yr old, menarche <12 yr old, menopause >55 yr old
- decreased risk with lactation, early menopause, early childbirth
- radiation exposure (e.g. mantle radiation for Hodgkin's disease)
- >5 yr HRT



Gender followed by age are the two greatest risk factors for breast cancer.

## Investigations

- mammography
  - indications:
    - ♦ screening refer to [Family Medicine](#), FM3
  - findings indicative of malignancy:
    - ♦ mass that is poorly defined, spiculated border
    - ♦ microcalcifications
    - ♦ architectural distortion
    - ♦ interval mammographic changes
    - ♦ normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies:
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
  - metastatic workup as indicated (usually after surgery or if clinical suspicion of metastatic disease): bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), head CT (only if specific neurological symptoms)



Any palpable dominant breast mass requires further investigation.



Diagnostic mammography is indicated in all patients, even in women <50 yr old.

## Diagnostic Procedures

- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- fine needle aspiration (FNA): for palpable solid masses; need experienced practitioner for adequate sampling
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

## Genetic Screening

- consider testing for BRCA1/2 if:
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer
  - young patient (<35 yr old)
  - bilateral breast cancer in patients <50 yr old

## Staging (see Table 20)

- clinical:
  - tumour size by palpation, mammogram
  - nodal involvement by palpation
  - metastasis by physical exam, CXR and abdominal U/S (or CT chest/abdomen/pelvis), bone scan (usually done post-op if node-positive disease)
- pathological:
  - tumour size
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear and mitotic grade
  - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, sentinel node positive/negative
  - estrogen receptor (ER) + progesterone receptor (PR) testing
  - Her2Neu receptor testing
  - margins: negative, <1 mm, positive
  - lymphovascular invasion (LVI)
  - extensive in situ component (EIC): DCIS in surrounding tissue
  - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIB

**Table 20. Staging of Breast Cancer (American Joint Committee on Cancer)**

Stage	Tumour	Nodes (regional) (clinical)	Metastasis	Survival (5-yr)
0	in situ	None	None	99%
I	<2 cm	None	None	94%
II A	<2 cm	Mobile ipsilateral	None	85%
II B	2-5 cm or >5 cm	None or mobile ipsilateral None	None None	70%
III A	Any size	Fixed ipsilateral or internal mammary	None	52%
III B	Skin/chest wall invasion	Any	None	48%
III C	Any size	Ipsilateral infraclavicular/internal mammary plus axillary nodes; ipsilateral supraclavicular node(s) ± axillary nodes	None	33%
IV	Any	Any	Distant	18%



Favourable Features	Unfavourable Features
<ul style="list-style-type: none"> <li>• &lt;2 cm</li> <li>• Grade I (low grade)</li> <li>• Node negative</li> <li>• ER positive</li> <li>• Mucinous pattern</li> </ul>	<ul style="list-style-type: none"> <li>• &gt;5 cm</li> <li>• Grade III (high grade)</li> <li>• Node positive</li> <li>• ER negative</li> <li>• Inflammatory cancer</li> <li>• Her2Neu positive</li> <li>• Positive margins</li> <li>• LVI</li> <li>• EIC</li> <li>• Dermal lymphatics involved</li> </ul>



## Pathology

- non-invasive (cannot penetrate basement membrane):
  - ductal carcinoma *in situ* (DCIS):
    - ♦ proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
    - ♦ 80% non-palpable, detected by screening mammogram
    - ♦ risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
    - ♦ treatment:
      - lumpectomy with wide excision margins + radiation (5-10% risk invasive cancer)
      - mastectomy if large area of disease, high grade or multifocal (risk of invasive cancer reduced to 1%)
      - possibly tamoxifen as an adjuvant treatment
      - 99% 5-yr survival
  - lobular carcinoma *in situ* (LCIS):
    - ♦ neoplastic cells completely contained within breast lobule
    - ♦ no palpable mass, no mammographic findings, usually incidental finding on breast biopsy for another indication
    - ♦ treatment
      - clinical follow-up
      - chemoprevention (tamoxifen)
      - surgery (uncommon)
    - ♦ not a precursor lesion, but considered a risk factor for breast cancer development
- invasive:
  - invasive ductal carcinoma (most common 80%):
    - ♦ originates from ductal epithelium and infiltrates supporting stroma
    - ♦ characteristics: hard, scirrhous, infiltrating tentacles, gritty on cross-section
  - invasive lobular carcinoma (8-15%):
    - ♦ originates from lobular epithelium
    - ♦ 20% bilateral (i.e. more often than infiltrating ductal carcinoma)
    - ♦ does not form microcalcifications, harder to detect mammographically (may benefit from MRI)
  - Paget's disease (1-3%):
    - ♦ ductal carcinoma that invades nipple with scaling, eczematoid lesion
  - inflammatory carcinoma (1-4%):
    - ♦ ductal carcinoma that invades dermal lymphatics
    - ♦ most aggressive form of breast cancer
    - ♦ clinical features: erythema, skin edema, warm, swollen and tender breast ± lump
    - ♦ peau d'orange indicates advanced disease (IIIB-IV)
  - male breast cancer (<1%):
    - ♦ most commonly invasive ductal carcinoma
    - ♦ often diagnosed at later stages
    - ♦ stage-for-stage similar prognosis to breast cancer in females
    - ♦ consider genetic testing
  - sarcomas: rare
    - ♦ most commonly Phyllodes tumour, a variant of fibroadenoma with potential for malignancy
    - ♦ can also be angiosarcomas – after previous radiation
  - lymphoma: rare
  - other: papillary, medullary, mucinous, tubular cancers
    - ♦ generally better prognosis

## Treatment

**Table 21. Breast Cancer Treatment by Stage**

Stage	Primary Treatment Options	Adjuvant Systemic Therapy
0 ( <i>in situ</i> )	BCS + radiotherapy BCS alone if margins > 1 cm and low nuclear grade Mastectomy* ± SLNB	None
I	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	May not be needed; discuss risks/benefits of chemotherapy and tamoxifen
II	BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SLNB	Chemotherapy for premenopausal women or postmenopausal and estrogen receptor (ER) negative, follow by tamoxifen if ER positive
III	Likely mastectomy + axillary node dissection + radiotherapy	Neoadjuvant therapy may be considered i.e. preoperative chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-op)
Inflammatory	Likely mastectomy + axillary node dissection + radiotherapy	Neoadjuvant therapy
IV	Surgery as appropriate for local control	Primary treatment is systemic therapy i.e. chemotherapy and/or hormone therapy

BCS = breast-conserving surgery; SLNB = sentinel lymph node biopsy

\*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient's preference since choice of local treatment does not significantly affect survival if local control is achieved



### Diagnosis of Breast Lesions: Fine-Needle Aspiration Cytology or Core Needle Biopsy?

#### A Review

*J Clin Pathol* 2012; 65:287-292

#### CNB

- High sensitivity (85%-100%) and specificity (86%-100%)
- High success rates for diagnosis of malignancy for palpable lesions (97%), non-palpable lesions (94%), and lesions <10 mm (90%)
- More accurate for histologic and immunohistochemistry examinations, and differentiation between *in situ* and invasive malignancies
- Reliable for testing of ER, PR, and HER2 status and proliferation assessment
- More painful procedure

#### FNAC

- Variable sensitivity (35%-95%) and specificity (48%-100%)
- Quality correlates with skill of aspirator
- Lower success rates for diagnosis of malignancy for palpable lesions (75-90%), non-palpable lesions (34-58%), and lesions <10 mm (50%)
- High rates of insufficient sampling for lesions >40 mm or calcified lesions
- Quick to perform
- Low technical costs

**Conclusions:** FNAC is preferable for palpable, low malignancy-risk lesions. However, for potential malignancies, CNB is advantageous with respect to prognostication and prediction and is likely cost-effective in the long-term.



Breast conserving surgery can be offered to most women with stage I/II disease.

### Primary Surgical Treatment

- breast-conserving surgery (BCS): lumpectomy with wide local excision
  - for treatment of stage I and II disease
  - must be combined with radiation for survival equivalent to mastectomy
  - contraindications:
    - ♦ high risk of local recurrence: extensive malignant-type calcifications on mammogram, multifocal primary tumours, or failure to obtain tumour-free margins after re-excision
    - ♦ contraindications to radiation therapy (pregnancy, previous radiation, collagen vascular disease)
    - ♦ large tumour size relative to breast
- mastectomy
  - radical mastectomy (rarely done anymore): removes all breast tissue, skin, pectoralis muscle, axillary nodes
  - modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
  - simple mastectomy: removes all breast tissue and skin
  - see [Plastic Surgery](#), PL32 for breast reconstruction
- axillary lymph node dissection (ALND)
  - performed if SLNB is positive or nodes are clinically concerning
  - risk of arm lymphedema (10-15%), decreased arm sensation, shoulder pain
- sentinel lymph node biopsy (SLNB)
  - technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
  - intraoperative frozen section
  - proceed with ALND if positive
  - 5% false negative rate

### Adjuvant/Neoadjuvant

- radiation
  - indications:
    - ♦ decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy (if >4 nodes positive or tumour >5 cm)
    - ♦ inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement
- hormonal
  - indications:
    - ♦ ER positive plus node-positive or high-risk node-negative
    - ♦ palliation for metastases
  - tamoxifen if premenopausal or aromatase inhibitors (e.g. anastrozole)
  - ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), androgens (e.g. fluoxymesterone) are other options
- chemotherapy
  - indications:
    - ♦ ER negative plus node-positive or high-risk node-negative
    - ♦ ER positive and young age
    - ♦ stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
    - ♦ palliation for metastatic disease

### Post-Treatment Follow-up

- visits q3-6mo x 2 yr and annually thereafter (frequency is controversial)
- annual mammography; no other imaging unless clinically indicated
- psychosocial support and counseling

### Local/Regional Recurrence

- recurrence in treated breast or ipsilateral axilla
- 1% per year up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

### Metastasis

- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation



#### Twenty-year Follow-up of a Randomized Study comparing Breast-conserving Surgery with Radical Mastectomy for Early Breast Cancer

*NEJM* 2002;16:1227-1232

**Background:** Women enrolled in a randomized trial to compare the efficacy of radical mastectomy (RM) with that of breast-conserving surgery (BCS) were followed over a 20-yr period for long-term outcomes including disease recurrence and survival.

**Methods:** From 1973-1980, 701 women with breast cancers measuring <2 cm in diameter were randomly assigned to undergo RM (n=349) or BCS followed by radiotherapy to the ipsilateral breast (n=352).

**Results:** Rates of ipsilateral disease recurrence were lower in patients treated with RM compared to BCS (crude cumulative incidence 2.3% versus 8.8% after 20 yr,  $P<0.001$ ). However, there was no significant difference in rates of contralateral breast malignancies, metastatic spread, or second primary malignancies between the two groups. All-cause mortality rates were 41.7% in the BCS group and 41.2% in the RM group ( $P=1.0$ ), with mortality rates due to breast cancer of 26.1% and 24.3% respectively ( $P=0.8$ ).

**Conclusion:** The long-term survival rate among patients treated with breast-conserving surgery and adjuvant radiotherapy is the same as that among patients treated with radical mastectomy.



There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I and II disease.

# Surgical Endocrinology

## Thyroid and Parathyroid

- see [Endocrinology](#), E20 and [Otolaryngology](#), OT34-OT37



### Thyroidectomy

- indications: thyroid cancer, symptomatic thyroid mass or goiter, medically refractory Graves' or hyperthyroidism
- contraindications: uncontrolled severe hyperthyroidism (i.e. Graves') due to risk of intraoperative or postoperative thyroid storm
- preoperative workup: thyroid ultrasound for thyroid nodules, fine needle aspiration for large nodules, ultrasound of the neck for lesions suspicious for papillary or medullary thyroid cancer, CT neck useful to rule out extension, vocal cord function
- complications: hypocalcemia secondary to hypoparathyroidism, recurrent/superior laryngeal nerve injury, neck hematoma, infection, thyrotoxic storm

### Parathyroidectomy

- indications: symptomatic primary hyperparathyroidism due to effects of PTH on bone or kidneys, asymptomatic primary hyperparathyroidism with specific laboratory criteria (elevated serum Ca, marked hypercalciuria, Cr clearance less than 30% normal, bone density reduction with T score less than 2.5, age less than 50)
- contraindications: familial hypocalciuric hypercalcemia
- preoperative workup:  $^{99m}\text{Tc}$  sestamibi scanning,  $\pm$  SPECT or CT, ultrasound
- complications: recurrent/superior laryngeal nerve injury, postoperative hypocalcemia, infection, bleeding

## Adrenal Gland

- see [Endocrinology](#), E29
- functional anatomy:
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine)
- types: functional (e.g. Cushing's syndrome, Conn's syndrome) or non-functional



### INCIDENTALOMA

- adrenal mass discovered by investigation of unrelated symptoms

### Epidemiology

- benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, kidney
- peak incidence of carcinoma: females age 50-60, risk decreases with increasing age and male gender

### Investigations

- MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
- functional studies:
  - pheochromocytoma: 24 h urine epinephrine, norepinephrine, metanephrine, normetanephrine, VMA (vanillylmandelic acid)
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, aldosterone:renin level, saline suppression test if appropriate
  - adrenal androgens: 17-OH progesterone, DHEAS
- FNA biopsy: if suspect metastasis to adrenal (must exclude pheochromocytoma first)
  - indicated if history of cancer or patient is smoker
- iodocholesterol scintigraphy: may distinguish benign vs. malignant disease

### Treatment

- functional tumour: resect
- non-functioning tumour:
  - >4 cm: resect
  - <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement

## Pancreas

### INSULINOMA

- tumour that secretes insulin
- most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

#### Clinical Features

- Whipple's triad
- palpitations, trembling, diaphoresis, confusion, seizure, personality changes

#### Investigations

- bloodwork: decreased serum glucose and increased serum insulin and C-peptide
- U/S, CT: insulinomas evenly distributed throughout head, body, tail of pancreas

#### Treatment

- only 10% are malignant
- enucleation of solitary insulinomas may be done endoscopically
- tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy



#### Whipple's Triad

- Symptomatic fasting hypoglycemia
- Serum glucose <50 mg/dL
- Relief of symptoms when glucose is administered

### GASTRINOMA

- tumour secreting gastrin; cause of Zollinger-Ellison syndrome

#### Clinical Features

- abdominal pain, peptic ulcer disease, severe esophagitis
- multiple ulcers in atypical locations refractory of antacid therapy

#### Investigations

- bloodwork: serum gastrin levels (usually >1000 pg/mL), secretin stimulation test
- U/S, CT: 70-90% found in Passaro's triangle (head of pancreas, duodenum, lymphatic bed posterior and superior to the duodenum)
- octreotide scintigraphy scan

#### Treatment

- 50% are malignant
- surgical resection of tumour dependent on location
- non-surgical treatment: chemotherapy, somatostatin analogues, interferon, chemoembolization
- if inoperable vagotomy can be performed for symptomatic control

### VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR

- tumour secreting vasoactive intestinal peptide (VIP); commonly located in the distal pancreas and most are malignant when diagnosed

#### Clinical Features

- severe watery diarrhea causing dehydration, weakness, electrolyte imbalance

#### Investigations


- bloodwork: serum VIP levels
- U/S, CT

#### Treatment

- somatostatin analogues
- surgical resection/palliative debulking

# Pediatric Surgery

Table 22. Pediatric Surgery

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical	Investigations	Treatment	Prognosis
<b>Hydrocele (see Urology, U28)</b> 	1-2% of live births Present at birth, majority close spontaneously by 1 yr M:F = 6:1 Prematurity	<b>Communicating hydroceles:</b> processus vaginalis fails to close with small opening for fluid to move freely between peritoneal cavity through patent processus (if opening progresses to allow passage of intestine, it is a hernia)  <b>Noncommunicating hydroceles:</b> fluid trapped in tunica vaginalis; in older children, may be secondary to testicular pathology (reactive hydrocele)	Painless scrotal mass Communicating hydroceles increase in size with standing or Valsalva, may be absent in the morning and large in the evening	Transillumination suggests hydrocele Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk	U/S if suspect pathology	Most resolve spontaneously by 1 yr Surgical repair if: – Persistence > 2 yr – Pain – Fluctuating in size which suggests communication – Cosmetic reasons – Infection	<2% recurrence
<b>Hypertrophic Pyloric Stenosis</b>	0.03-1.0% of live births Can present at 1-20 wk, most commonly at 6-8 wk M:F = 4:1 Early erythromycin exposure (<13 d old)	Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction Hypovolemia caused by emesis of gastric content causes hypochloremic hypokalemic metabolic alkalosis. Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria	Projectile non-bilious vomiting Vomiting 30-60 min after feeds Hungry after vomiting Dehydration (variable severity)	Smooth oblong 1-2 cm mass palpable above umbilicus, "olive" Visible left-to-right gastric contraction "waves" after feeding	Electrolytes (assess hypochloremia, dehydration) U/S shows pyloric length > 14 mm, muscle thickness > 4 mm Upper GI series necessary only when U/S unavailable or non-diagnostic will show "string sign"	Fluid resuscitate with normal saline, correct electrolyte and acid/base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate. NG tube decompression unnecessary Pyloromyotomy, open (Ramstedt vs. transumbilical or laparoscopic approach) Alternative therapies such as TPN/wait or atropine impractical due to long time course of effect	Pyloromyotomy curative
<b>Congenital Diaphragmatic Hernias</b> 3 types: – Posterolateral (Bochdalek) – Left-sided, 85% – Right-sided, 13% – Bilateral, rare, often fatal – Anterior (Morgagni) – Hiatus	1 in 2000 to 5000 live births Presents within hours of life although some cases of delayed presentation M = F >10% are associated with other congenital anomalies Prenatal diagnosis common	<b>Left-sided:</b> small bowel, large bowel, stomach and solid viscera (spleen, left lobe of liver) herniate into thorax  <b>Right-sided:</b> liver, large bowel herniate into thorax Pulmonary hypoplasia Pulmonary hypertension	Early respiratory distress Cyanosis Scaphoid abdomen Prenatal diagnosis	Decreased air entry ± bowel sounds in the chest Displaced heart sounds	Prenatal US/MRI ABG CXR (bowel loops in hemithorax, shifted heart) Echocardiography Genetic consultation if warranted	Intubate Orogastric suction Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extracorporeal membrane oxygenation). Surgical repair after stable by hernia reduction and closure of diaphragmatic defect – open vs. thoracoscopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect	Later presentations have better outcomes Hearing deficit (40%) Associated GERD MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy.  Need for long term surveillance for potential recurrence Failure to thrive Chronic lung disease if severe hypoplasia



**Hypertrophic Pyloric Stenosis**  
 Non-bilious emesis in infant is the classic presentation.

**Table 22. Pediatric Surgery** (continued)

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical	Investigations	Treatment	Prognosis
<b>Meckel's Diverticulum</b> Most common remnant of vitelline duct that connects yolk sac with primitive midgut	1-3% of population M:F = 3:1 Present most frequently first 5 yr of life Symptomatic in 2% of cases	Failure of vitelline duct to regress 5-7 wk in utero; 50% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphalomesenteric fistula, umbilical sinus, umbilical cyst, fibrous band	Bright red blood per rectum (heterotopic gastric mucosa in Meckel's causing mucosal ulceration and bleeding in adjacent small bowel mucosa) Abdominal sepsis (Meckel's diverticulitis ± perforation) Small bowel volvulus around fibrous band	Tenderness (lower abdomen) near umbilicus	AXR Meckel scan: scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 85%, specificity 95%)	Stabilize, resection by laparotomy or laparoscopy ± incidental appendectomy	Resection curative
<b>Malrotation</b>	1:500 live births 1/3 present by 1 wk of age, 3/4 by 1 mo of age, 90% by 1 yr of age M:F = 1:1; higher incidence among patients with cardiac anomalies, heterotaxy syndromes	Failure of gut to normally rotate around superior mesenteric artery with associated abnormal intestinal attachments and anatomic positions Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high risk for volvulus)	Bilious emesis is THE cardinal sign, especially if abdomen nondistended. If bilious emesis in ill child with distend abdomen, consider surgical exploration to rule out volvulus. Rectal bleed (late/o minous signs) Intermittent symptoms	Bilious drainage from NG tube Tachycardic, pale Diaphoretic Flat abdomen Tenderness	AXR: obstruction of proximal small bowel, double-bubble sign, intestinal wall thickened Immediate UGI: dilated duodenum, duodenojejunal segment (Ligament of Treitz) right of midline and not fixed posteriorly over spinal column, "corkscrew" sign indicating volvulus U/S: "whirlpool" sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies	IV antibiotics Fluid resuscitation <b>EMERGENT LAPAROTOMY</b> Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd's bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide congenital adhesions), ± appendectomy Positioning the bowel into non-rotation (small bowel in right abdomen, large bowel in left abdomen)	Mortality related to length of bowel loss: 10% necrosis – 100% survival rate, 75% necrosis – 35% survival rate Recurrence 2-6%
<b>Gastroschisis</b>	1:2000 live births Antenatal diagnosis common Increases with younger maternal age and associated with IUGR M:F = 1:1	Defect of abdominal wall, with free extrusion of intestine into amniotic cavity No specific environmental factor identified Defect in embryogenesis unclear	Not associated with genetic syndromes 10% with intestinal atresia Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel	Hollow viscera (stomach, small and large bowels) Defect lateral to cord (usually right) Bowel may be inflamed, thickened, matted, foreshortened Defect size variable	Prenatal ultrasound, elevated MS-AFP	NG decompression IV fluids IV antibiotics Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo May have bowel dysmotility requiring motility medications	> 90% survival rate
<b>Omphalocele</b>	1:5000 live birth Antenatal diagnosis common Lower gestational age Increased maternal age M:F = 1.5:1	Defect of abdominal wall, with extrusion of sac covered viscera (amnion, Wharton's jelly, peritoneum) Duhamel's theory – failure of body wall morphogenesis	Associated with genetic syndromes 30-70% (e.g. Pentalogy of Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome) Associated pulmonary hypoplasia	Hollow viscera (stomach, small and large bowels, often liver) Cord on the sac	Prenatal ultrasound Elevated MS-AFP	NG decompression IV fluids IV antibiotics Small defect (<2 cm): Primary closure Medium (2-4 cm) and large (> 4 cm) defects best treated with silver sulfadiazine to promote epithelialization coupled with compression dressing to allow gradual reduction, followed by future repair with or without mesh	40-70% survival rate Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles



Bilious vomiting in infant is a life-threatening emergency secondary to midgut volvulus until proven otherwise.



#### Rule of 2s for Meckel's Diverticulum


- 2% of the population
- 2:1 male-to-female ratio
- Symptomatic in 2% of cases
- Found within 2 feet (10-90 cm) of the ileocecal (IC) valve
- 2 inches in length
- 2 inches in diameter
- 2 types of tissue (gastric, pancreatic)
- Often present by 2 yr of age



Table 22. Pediatric Surgery (continued)

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical	Investigations	Treatment	Prognosis
<b>Umbilical Hernias</b>	Incidence 2-14% Increases with prematurity Decreases with increasing age	Incomplete closure of peritoneal and fascial layers within umbilicus by 5 yr	Majority asymptomatic Majority spontaneously resolve by age 5 Incarceration prior to age 5 very rare Most symptoms occur in late adolescence or adulthood	Protrusion from umbilicus Important to differentiate from less common abdominal wall hernias that don't spontaneously resolve (e.g. epigastric hernias) Most umbilical fascial defects > 1.5 cm in infancy will not close spontaneously	None if uncomplicated	Repair if not spontaneously closed by age 5 Earlier repair of large "proboscoid" hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect	Low risk of recurrence
<b>Intestinal Atresia</b>	Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or "double-bubble" sign on x-ray for duodenal atresia Decreasing with increasing age	Duodenal – failure of bowel to recanalize after endodermal epithelium proliferation (wk 8-10) Jejunum/ileal – acquired as result of vascular disruption → ischemic necrosis → resorption of necrotic tissue → blind distal and proximal ends Colon – mechanism unknown, thought to be similar to small bowel atresia	Gastric distension and vomiting (usually bilious) Duodenal – may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal and vertebral anomalies), 24-28% have Down syndrome Jejunum/ileal – within 2 d of birth, may be associated with cystic fibrosis Colonic – within 3 d of birth	Complete physical Special notice to abdominal exam Perineum and anus Include evaluation of respiratory distress and signs of volume depletion Congenital anomalies Jaundice	Contrast enema ± UGI with small bowel follow through (SBFT) Group and screen INR and PTT if for surgery	NPO NG tube decompression Fluid resuscitate TPN Broad spectrum antibiotics Duodenal – duodenoduodenostomy or duodenojejunostomy Jejunum/ileal – primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures Colonic – primary anastomosis	Long term survival Duodenal – 86% Jejunum/ileal – 84% Colonic – 100%
<b>Hirschsprung's Disease</b>	1:5000 births M:F = 3:1-4:1, approaches 1:1 when whole colon involved Can have aganglionosis of small bowel as well Familial Hirschsprung's in <5% of cases	Defect in migration of neurocrest cells to intestine resulting in aganglionic bowel that fails to peristalt and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively; always starts in the rectum and variable involvement proximally; RET mutation	Failure to pass meconium spontaneously within 48 h of life is the classic history (95% of normal children should pass meconium within 24 h, and the remaining 5% within 48 h). Symptoms of bowel obstruction: abdominal distension, constipation, bilious emesis Enterocolitis/sepsis Failure to thrive	± abdominal distension Squirt/blast sign	Rectal biopsy (gold standard) – look for aganglionosis and neural hypertrophy AXR Contrast enema to find narrow rectum and transition zone. Anal manometry unreliable in infants – classic finding is absence of rectoanal inhibitory reflex	Surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis	Most have normal/near-normal anorectal function Complications: Fecal incontinence and constipation, post-operative enterocolitis (medical emergency if progresses to sepsis)
<b>Cryptorchidism</b>	2-5% of term males – most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend	Idiopathic Descent is mediated by descendin which is created in response to testosterone Descent usually begins at 28 wk	Palpable testicle within inguinal canal or testicle which can be milked down into scrotum (called retractile testis) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities	Bi-annual testicular exam with palpation Distinguish truly undescended testis from retractile testis (which is "high" testis due to hyperactive cremasteric muscles)	Depends on age of presentation U/S or MRI exam if no palpable testis Older child: LH, FSH, MIS, hCG stimulation test for gonadotropin production Infant: U/S, FSH, LH, karyotype, MIS, 17-Hydroxyprogesterone	hCG to stimulate testosterone production and descent Orchidopexy – especially if undescended by age 6 mo-2 yr	Orchidopexy Decreased risk of torsion and blunt trauma to testicle No effect on malignant potential of testicle Descent can preserve spermatogenesis if performed by 1 yr of age 1/1000 risk for testicular cancer (population risk is 1/4000)

Table 22. Pediatric Surgery (continued)

Condition	Epidemiology and Risk Factors	Pathophysiology	Clinical Features and History	Physical	Investigations	Treatment	Prognosis
<b>Intussusception</b>	Most common cause of bowel obstruction between the ages of 6-36 mo 26/100,000 newborns More common males (3:2) Pathologic lead points: enlarged Peyer's patches due to viral infections of the GI tract, polyps, Meckel's diverticulum CF, lymphoma, IBD may increase risk	Idiopathic is most common Usually starts at ileocecal junction Telescoping of bowel into itself causing an obstruction and vascular compromise	Acute onset of abdominal pain which is classic episodic "colicky" pain Vomiting ± bilious Abdominal mass Currant-jelly stool suggests mucosal necrosis and sloughing	Abdominal exam Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness Signs of bowel obstruction- distended abdomen Look for localized peritonitis which suggests transmural ischemia	AXR for signs of bowel obstruction or perforation U/S if suspect pathology	If peritonitis, then consider operative management Non-operative management involves reduction via air contrast enema Operative reduction can be done open or laparoscopically Resection of involved colon if failure to reduce or bowel appears compromised	10% recurrence rate If recurrent = more likely non-idiopathic In successfully reduced by enema in older children allow 2 wk resolution of edema then perform SBT to rule out pathologic lead points
<b>Tracheoesophageal Fistula (TEF)</b>	1:3000-1:4500	Associated anomalies in 50%: VACTERL association (see <a href="#">Pediatrics</a> , P41) 	Varies with type of fistula May have history of maternal polyhydramnios, May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds, respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth and nose that return after suctioning,		X-ray: anatomic abnormalities, NG tube curled in pouch	Investigate for other congenital anomalies, early repair by surgical ligation to prevent lung damage and maintain nutrition and growth	Complications: pneumonia, sepsis, reactive airways disease. Following repair: esophageal stenosis and strictures at repair site, gastroesophageal reflux and poor swallowing (i.e. dysphagia, regurgitation)
<b>Inguinal Hernias</b>	5% of all term newborns 2x risk and more likely bilateral if pre-term More common in males (4:1) Low birth weight increases risk 1/5 inguinal hernias will become incarcerated if patient is <1 yr old Incarceration is more common in females Associated with other conditions: androgen insensitivity, connective tissue diseases	All infant hernias are indirect: Descent of intra-abdominal contents through the internal inguinal ring through a patent tunica vaginalis	Most common presentation: painless intermittent mass in groin, may also note extension into scrotum (scrotal mass in absence of inguinal mass is a hydrocele) If incarcerated: tender, vomiting, firm mass, erythema then cyanosis of mass may be noted	Palpate for "bag of worms" suggests possible testicular varicocele Biannual testicular exam + palpation along inguinal canal to evaluate for any masses "Silk sign" – palpable thickening of cord Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen Must always try reduction to confirm that hernia is not incarcerated	Physical exam is gold standard U/S only if physical exam uncertain (e.g. in small infants where exam can be difficult)	Manual reduction – to relieve acute symptoms Herniorrhaphy – definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias Laparoscopic or open techniques	Risk of recurrence after surgical reduction <3% but higher if repair done in premature infants or if hernia was incarcerated/strangulated at repair

## Skin Lesions

- see [Dermatology](#), D5; [Emergency](#), ER17; [Plastic Surgery](#) PL5



All inguinal hernias of infancy and childhood require repair at the earliest convenience. Emergent repair if incarcerated/strangulated!

## Common Medications

<b>Antiemetics</b>	<ul style="list-style-type: none"> <li>dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6h prn</li> <li>prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM bid-tid prn</li> <li>metoclopramide (Maxeran®) 10 mg IV/IM q2-3h prn, 10-15 mg PO qid (30 min before meals and qhs)</li> <li>ondansetron (Zofran®) 4-8 mg PO q8h prn</li> <li>granisetron (Kytrel®) 1 mg PO bid (for nausea from chemotherapy/radiation)</li> </ul>
<b>Analgesics</b>	<ul style="list-style-type: none"> <li>acetaminophen ± codeine (Tylenol® #3/plain) 1-2 tabs q4-6h PO/PR prn</li> <li>morphine 2.5-10 mg IM/SC q 4-6h prn + 1-2 mg IV q1h prn for breakthrough</li> <li>ketorolac (Toradol®) 30-60 mg IM/IV q6h prn</li> <li>Percocet® (acetaminophen/oxycodone, 325/5 mg) 1-2 tabs PO q4-6h prn</li> </ul>
<b>DVT Prophylaxis</b>	<ul style="list-style-type: none"> <li>heparin 5000 units SC bid, if cancer patient then heparin 5000 units SC tid</li> <li>dalteparin (Fragmin®) 5000 units SC daily</li> <li>enoxaparin (Lovenox®) 40 mg SC daily</li> </ul>
<b>Antidiarrheals</b>	<ul style="list-style-type: none"> <li>loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d</li> <li>diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO qid</li> </ul>
<b>Laxatives</b>	<ul style="list-style-type: none"> <li>sennosides (Senokot®) 1-2 tabs qhs</li> <li>docusate sodium (Colace®) 100 mg PO bid</li> <li>glycerine suppository 1 tab PR prn</li> <li>lactulose 15-30 mL PO qid prn</li> <li>milk of magnesia (MOM) 30-60 mL PO qid prn</li> <li>bisacodyl (Dulcolax®) 10-15 mg PO prn</li> </ul>
<b>Sedatives</b>	<ul style="list-style-type: none"> <li>zopiclone (Imovane®) 5-7.5 mg PO qhs prn</li> <li>lorazepam (Ativan®) 0.5-2 mg PO/SL qhs prn</li> </ul>
<b>Antibiotics</b>	<ul style="list-style-type: none"> <li>cefazolin (Ancef®) 1 g IV/IM on call to OR or q8h – GP except <i>Enterococcus</i>, GN only <i>E. coli</i>, <i>Klebsiella</i> and <i>Proteus</i></li> <li>cefalexin (Keflex®) 250-500 mg PO qid – <i>Listeria</i>, GP except <i>Enterococcus</i>, GN only <i>E. coli</i>, <i>Klebsiella</i> and <i>Proteus</i></li> <li>ceftriaxone 1-2 g IM/IV q24h – broad coverage including <i>Pseudomonas</i></li> <li>ampicillin 1-2 g IV q4-6h – <i>Listeria</i>, GP (<i>Enterococcus</i>) except <i>Streptococcus</i> and <i>E. coli</i>, oral anaerobes except <i>Bacteroides</i></li> <li>gentamicin 3-5 mg/kg/d IM/IV divided q8h; monitor creatinine, gentamicin levels – GN including <i>Pseudomonas</i></li> <li>ciprofloxacin 400 mg IV q12h, 500 mg PO bid – GN including <i>Pseudomonas</i></li> <li>metronidazole (Flagyl®) 500 mg PO/IV bid, (500 mg PO tid for <i>C. difficile</i>) – anaerobes</li> <li>clindamycin 600-900 mg IV q8h, 150-400 mg PO qid – GP except <i>Enterococcus</i>, anaerobes</li> </ul>
<b>Over-the-Counter Medications</b>	<ul style="list-style-type: none"> <li>Pepto-Bismol® (bismuth subsalicylate) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d side effects: black stools, risk of Reye's syndrome in children</li> <li>Alka-Seltzer® (ASA + citrate + bicarbonate) 2 tabs in 4 oz water PO q4h prn, max 8 tabs</li> <li>Maalox® (aluminum hydroxide + magnesium hydroxide) 10-20 mL or 1-4 tabs PO prn</li> <li>Tums® (calcium carbonate) 1-3 g PO q2h prn</li> <li>Rolaids® (calcium carbonate and magnesium hydroxide) 2-4 tabs PO q1h prn, max 12 tabs/d</li> </ul>

## References

- Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical site infections. *Ann Surg* 2001;253:1082-1093.
- Andersen BR, Kallehave FL, Andersen HK. Antibiotics versus placebo for prevention of postoperative infection after appendicectomy. *Cochrane DB Syst Rev* 2005;3:CD001439.
- Andreoli TE et al. Cecil essentials of medicine, 5th ed. Philadelphia: WB Saunders, 2001.
- Antimicrobial prophylaxis for surgery. *Treat Guidel Med Lett* 2009;7:47-52.
- Applegate KE. Intussusception in children: evidence-based diagnosis and treatment. *Pediatr Radiol* 2009;39(Suppl 2):S140-143.
- Barra Ade A, Gobbi H, de L Rezende CA, Gouvêa AP, de Lucena CE, Reis JH, Costa e Silva SZ. A comparison of aspiration cytology and core needle biopsy according to tumor size of suspicious breast lesions. *Diag Cytopathol* 2008;36:26-31.
- Bartlett LC. Pressure necrosis is the primary cause of wound dehiscence. *Can J Surg* 1985;28:27-30.
- Bateson MC. Gallbladder disease. *BMJ* 1999;318:1745-1748.
- Bazarah BM, Peltekian KM, McAlister VC et al. Utility of MELD and child-turcotte-pugh scores and the canadian waitlisting algorithm in predicting short-term survival after liver transplant. *Clin Invest Med* 2004;27:162-167.
- Bland KI, et al. The practice of general surgery, 1st ed. Toronto: WB Saunders, 2002.
- Brandt ML. Pediatric hernias. *Surg Clin N Am* 2008;88:27-43,vii-viii.
- Bruniciardi FC et al. Schwartz's principles of surgery, 9th ed. McGraw-Hill, 2010.
- Canadian Task Force on Preventive Health Care. Colorectal cancer screening. *CMAJ* 2001;165:206-208.
- Chandler C, et al. Prospective evaluation of early versus delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. *Am J Surg* 2000;66:896-900.
- Chapman WP, Herrera R, Jones CM. A comparison of pain produced experimentally in lower esophagus, common bile duct, and upper small intestine with pain experienced by patients with diseases of biliary tract and pancreas. *Surg Gynecol Obstet* 1949;89:573-582.
- Classen DC et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *NEJM* 1992;326:281-286.
- Coha M, Cerutti E, Schellino MM, Biolino P, Occeila P, Belloni G, Villanis G, Fiore G, Cavallo F, Ranieri VM; Piedmont Intensive Care Units Network (PICUN). Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. *JAMA* 2005;293:589-595.
- Colquitt JL, Picot J, Loveman E, Clegg AJ. Surgery for obesity. *Cochrane DB Syst Rev* 2009;2:CD003641.
- Darwish MS, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 143:88-98.e3.
- Dodson MK, Magann EF, Meeks GR. A randomized comparison of secondary closure and secondary intention in patients with superficial wound dehiscence. *Obstet Gynecol* 1992;80:321-324.
- Hutson JM, Balic A, Nation T, Southwell B. Cryptorchidism. *Semin Pediatr Surg* 2010; 19:215-224.
- Darouiche RO et al. Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis. *NEJM* 2010;362:18-26.
- De Groen PC et al. Biliary tract cancers. *NEJM* 1999;341:1368-1378.

- Doherty GM. Current surgical diagnosis and treatment, 12th ed. New York: McGraw-Hill, 2006.
- Eagon JC, Miedema BW, Kelly KA. Postgastrectomy syndromes. *Surg Clin N Am* 1992;72:445.
- Edell SL and Eisen MD. Current imaging modalities for the diagnosis of breast cancer. *Delaware Med J* 1999;71:377-382.
- Ferzoco LB et al. Acute diverticulitis. *NEJM* 1998;338:1521-1526.
- Fishman A, Martinez F, Nangunheim K, Piantadosi S, Wise R, Ries A, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *NEJM* 2003;348:2059-2073.
- Fitzgibbons RJ Jr, Giobbie-Hurder A, Gibbs JO, Dunlop DD, Reda DJ, McCarthy M Jr, et al. Watchful waiting vs. repair of inguinal hernia in minimally symptomatic men: a randomized clinical trial. *JAMA* 2006;295:285-292.
- García-Miguel FJ, Serrano-Aguilar PG, López-Bastida J. Preoperative assessment. *Lancet* 2003;362(9397):1749.
- Germani G, Gurusamy K, Gercovich M, Toso C, Fede G, Hemming A, Suh KS, Weber A, Burroughs AK. Which matters most: number of tumors, size of the largest tumor, or total tumor volume? *Liver Transplant* 2011;Suppl2:S58-66.
- Gibril F, Reynolds JC, Lubensky JA, Roy PK, Peghini PL, Doppman JL, Jensen RT. Ability of somatostatin receptor scintigraphy to identify patients with gastric carcinoids: a prospective study. *J Nucl Med* 2000;41:1646-1656.
- Glasgow RE, Mulvihill SJ. Postgastrectomy syndromes. *Probl Gen Surg* 1997;14:132-152.
- Goldhirsch A, et al. Meeting highlights: International Consensus Panel on the treatment of primary breast cancer. *J Clin Oncol* 2001;19:3817-3827.
- Graham DJ, McHenry CR. The adrenal incidentaloma: guidelines for evaluation and recommendations for management. *Surg Onc Clin N Am* 1998;7:749-764.
- Gurusamy KS, Samraj K, Fusai G, Davidson BR. Early versus delayed laparoscopic cholecystectomy for biliary colic. *Cochrane DB Syst Rev* 2008;4:CD007196.
- Harken AH and Moore EE. Abemathy's surgical secrets. Philadelphia: Hanley and Belfus, 2000.
- Hartmann LC et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *NEJM* 1999;340:77-84.
- Hilditch WG, Asbury AJ, Jack E, McGrane S. Validation of a pre-anaesthetic screening questionnaire. *Anaesthesia* 2003;58:874-877.
- Hong Z, Wu J, Smart G, Kaita K, Wen SW, Paton S, Dawood M. Survival analysis of liver transplant patients in Canada 1997-2002. *Transplant P* 2006;38(9):2951-2956.
- Hortobagyi GN. Treatment of breast cancer. *NEJM* 1998;339:974-984.
- Ingraham AM, Cohen ME, Bilimoria KY, Ko CY, Hall BL, Russell TR, Nathens AB. Effect of delay to operation on outcomes in adults with acute appendicitis. *Arch Surg* 2010;145:886-892.
- Ivanovitch JL et al. A practical approach to familial and hereditary colorectal cancer. *Am J Med* 1999;107:68-77.
- Janne PA et al. Chemoprevention of colorectal cancer. *NEJM* 2000;342:1960-198.
- Jesus EC, Karliczek A, Matos D, Castro AA, Atallah AN. Prophylactic anastomotic drainage for colorectal surgery. *Cochrane DB Syst Rev* 2004;4:CD002100.
- Johnson CD. Upper abdominal pain: gallbladder. *BMJ* 2001;323:1170-1173.
- Kanwal F, Dulai GS, Spiegel BMR et al. A comparison of liver transplantation outcomes in the pre- vs. post-MELD eras. *Aliment Pharm Ther* 2005;21:169-177.
- Kasper, Dennis L. Harrison's principles of internal medicine, 16th ed. 2005.
- Kehlet H et al. Review of postoperative ileus. *Am J Surg* 2001;182(Suppl):3S-10S.
- Kemeny MM, Adak S, Gray B, Macdonald JS, Smith T, Lipsitz S, Sigurdson ER, O'Dwyer PJ, Benson AB 3rd. Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy – an intergroup study. *J Clin Oncol* 2002;20:1499-1505.
- King JE et al. Care of patients and their families with familial adenomatous polyposis. *Mayo Clin Proc.* 2000;75:57-67.
- Kosters JP, Gotzsche PC. Regular self-examination or physical examination for early detection of breast cancer. *Cochrane Library.* 2002;Issue 2.
- Latif A. Gastric cancer update on diagnosis, staging and therapy. *Postgrad Med* 1997;102:231-236.
- Lawrence PF. Essentials of general surgery. Philadelphia: Lippincott Williams & Wilkins, 2000.
- Levine CD. Toxic megacolon: diagnosis and treatment challenges. *AACN Clinical Issues* 1999;10:492-499.
- Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. *JAMA* 2003;289:1421-1424.
- Lickstein IH, Matthews JB. Elective surgical management of peptic ulcer disease. *Probl Gen Surg* 1997;14:37-53.
- Madan AK et al. How early is early laparoscopic treatment of acute cholecystitis? *Am J Surg* 2002;183:232-236.
- Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *NEJM* 1993;328:1365-1371.
- Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult blood screening on the incidence of colorectal cancer. *NEJM* 2000;343:1603-1607.
- Mamounas EP. NSABP breast cancer clinical trials: recent results and future directions. *Clin Med Res* 2003;1:309-326.
- Martin RF, Rossi RL. The acute abdomen: an overview and algorithms. *Surg Clin N Am* 1997;77:1227-1243.
- McDonnell SK. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. *J Clin Oncol* 2001;19:38-43.
- Olivotto I, Levine M. Clinical practice guidelines for the care and treatment of breast cancer: the management of ductal carcinoma in situ (summary of the 2001 update). *CMAJ* 2001;165:912-913.
- Olsen O, Gotzsche PC. Screening for breast cancer with mammography (Cochrane review) the Cochrane Library 2003;Issue 3. Oxford: Update Software.
- Paulsan, EK et al. Suspected appendicitis. *NEJM* 2003;348:236-242.
- Paulson EK, Kalady MF, Pappas TN. Suspected Appendicitis. *NEJM* 2003;348:236-242.
- Polk H, Christmas B. Prophylactic antibiotics in surgery and surgical wound infections. *Am Surgeon* 2000;66:105-111.
- Preoperative antibiotic prophylaxis. CDC. Available from: <http://www.cdc.gov/ncidod/hip/SSI/SSI.pdf>.
- Ransohoff DF and Sandler RS. Screening for colorectal cancer. *NEJM* 2002;346:40-44.
- Ray BS, Neill CL. Abdominal visceral sensation in man. *Ann Surg* 1947;126:709-723.
- Ringash J. Preventive health care, 2001 update: screening mammography among women aged 40-49 years at average risk of breast cancer. *CMAJ* 2001;164:469-476.
- Ross NS and Aron DC. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. *NEJM* 1990;323:1401-1405.
- Roy MA. Inflammatory bowel disease. *Surg Clin N Am* 1997;77:1419-1431.
- Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. *Lancet* 2007;369:1731-1741.
- Rustgi AK. Hereditary gastrointestinal polyposis and nonpolyposis syndromes. *NEJM* 1994;331:1694-1702.
- Sandhu L, Sandroussi C, Guba M, Selzner M, Ghanekar A, Cattal MS, McGilvray ID, Levy G, Greig PD, Renner EL, Grant DR. Living donor liver transplantation versus deceased donor liver transplantation for hepatocellular carcinoma: comparable survival and recurrence. *Liver Transplant* 2012;18:315-322.
- Saini S. Imaging of the hepatobiliary tract. *NEJM* 1997;336:1889-1894.
- Sauerland S, Jaschinski T, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane DB Syst Rev* 2010;10:CD001546.
- Sheth SG and LaMont JT. Toxic megacolon. *Lancet* 1998;351:509-513.
- Simeone DM, Hassan A, Scheiman JM. Giant peptic ulcer: a surgical or medical disease? *Surgery* 1999;126:474-478.
- Styblo TM, Wood WC. The management of ductal and lobular breast cancer. *Surg Oncol* 1999;8:67-75.
- The University of Cincinnati Residents. The mont reid surgical handbook. St. Louis: Mosby, 1997.
- Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? *JAMA* 2003;289:80-86.
- Veronesi U, et al. twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *NEJM* 2002;16:1227-1232.
- Waki, K. UNOS Liver Registry: ten year survivals. *Clin Transplant* 2006:29-39.
- Way, LW. Current surgical diagnosis and treatment, 11th ed. 2003.
- Yadav D, Agarwal N, Pitchumoni CS. A critical evaluation of laboratory tests in acute pancreatitis. *Am J Gastroenterol* 2002;97:1309-1318.

Evelyn Cheung and Christopher Yarnell, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Barry J. Goldlist, staff editor

<b>Seniors in Canada and the U.S. ....</b>	<b>2</b>	<b>Driving Competency ....</b>	<b>10</b>
Health Status		Reporting Requirements	
<b>Physiology and Pathology of Aging ....</b>	<b>2</b>	Conditions that may Impair Driving	
<b>Differential Diagnoses of Common</b>		<b>Health Care Institutions ....</b>	<b>11</b>
<b>Presentations ....</b>	<b>3</b>	<b>Palliative and End-of-Life Care ....</b>	<b>12</b>
Constipation		Principles and Quality of Life	
Delirium, Dementia and Depression		End-of-Life Care Discussions	
Elder Abuse		Power of Attorney	
Falls		Instructional Advance Directives	
Frailty (Failure to Thrive)		Symptom Management	
Incontinence		<b>Geriatric Pharmacology. ....</b>	<b>13</b>
Gait Disorders		Pharmacokinetics	
Hazards of Hospitalization		Pharmacodynamics	
Hypertension		Polypharmacy	
Immobility		Inappropriate Prescribing in the Elderly	
Immunizations		<b>Common Medications ....</b>	<b>15</b>
Malnutrition		<b>Landmark Geriatric Trials ....</b>	<b>16</b>
Osteoporosis		<b>References ....</b>	<b>17</b>
Presbycusis			
Pressure Ulcers			

## Acronyms

ACEI	angiotensin converting enzyme inhibitor	FAP	familial adenomatous polyposis	NE	norepinephrine
ARB	angiotensin receptor blocker	GCA	giant cell arteritis	NSTEMI	non-ST elevation myocardial infarction
BPH	benign prostatic hypertrophy	HR	heart rate	PPI	proton pump inhibitor
CABG	coronary artery bypass graft	IBD	inflammatory bowel disease	PPS	palliative performance scale
CHF	congestive heart failure	IBS	irritable bowel syndrome	PTH	parathyroid hormone
CO	cardiac output	ICP	intracranial pressure	RA	rheumatoid arthritis
CVA	cerebrovascular accident	LOC	level of consciousness	SLE	systemic lupus erythematosus
DHPCCB	dihydropyridine calcium channel blocker	MMSE	mini mental status examination	UTI	urinary tract infection
ESAS	Edmonton symptom assessment scale				

# Seniors in Canada and the U.S.

## Health Status

**Table 1. Causes of Mortality and Morbidity in Canadian and American Seniors**

Mortality (Can <sup>1</sup> /U.S. <sup>2</sup> )	Morbidity <sup>1,2</sup>
1. Diseases of the heart and circulatory system (30.0/27.0%)	1. Hypertension
2. Malignant neoplasms (20.0/22.0%)	2. Arthritis
3. Cerebrovascular disease (8.0/6.0%)	3. Heart disease
4. Chronic lower respiratory disease (5.1/7.0%)	4. Diabetes
5. Accidents (2.9%)	5. Ulcers
6. Alzheimer's (4.2/5.0%)	6. Stroke
	7. Asthma
	8. Allergies

<sup>1</sup>Statistics Canada, 2005    <sup>2</sup>Minino AM, 2009



### Geriatric Giants

- Memory
- Falls
- Incontinence
- Polypharmacy



### 5 Is of Geriatrics

- Immobility
- Intellect
- Incontinence
- Iatrogenesis
- Impaired homeostasis

## Physiology and Pathology of Aging

### Definition

- major categories of impairment that appear with old age and affect the physical, mental and social domains of the elderly, usually due to many predisposing and precipitating factors, rather than a single cause

**Table 2. Changes Occurring Frequently with Aging**

System	Physiological Changes	Pathological Changes
<b>Neurologic</b>	Decreased wakefulness, brain mass, cerebral blood flow	Increased insomnia, neurodegenerative disease, stroke, decreased reflex response
<b>Special Senses</b>	Decreased lacrimal gland secretion, lens transparency, dark adaptation, decreased sense of smell and taste	Increased glaucoma, cataracts, macular degeneration, presbycusis, presbyopia, tinnitus, vertigo, oral dryness
<b>Cardiovascular</b>	Increased sBP, dBP, decreased HR, CO Decreased vessel elasticity, cardiac myocyte size and number, $\beta$ -adrenergic responsiveness	Increased atherosclerosis, CAD, MI, CHF, hypertension, arrhythmias
<b>Respiratory</b>	Increased tracheal cartilage calcification, mucous gland hypertrophy Decreased elastic recoil, mucociliary clearance, pulmonary function reserve	Increased COPD, pneumonia, pulmonary embolism
<b>Gastrointestinal</b>	Increased intestinal villous atrophy Decreased esophageal peristalsis, gastric acid secretion, liver mass, hepatic blood flow, calcium and iron absorption	Increased cancer, diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction
<b>Renal and Urologic</b>	Increased proteinuria, urinary frequency Decreased renal mass, creatinine clearance, urine acidification, hydroxylation of vitamin D, bladder capacity	Increased urinary incontinence, nocturia, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI
<b>Reproductive</b>	Decreased androgen, estrogen, sperm count, vaginal secretion Decreased ovary, uterus, vagina, breast size	Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis
<b>Endocrine</b>	Increased NE, PTH, insulin, vasopressin Decreased thyroid and adrenal corticosteroid secretion	Increased DM, hypothyroidism, stress response
<b>Musculoskeletal</b>	Increased calcium loss from bone Decreased muscle mass, cartilage	Increased arthritis, bursitis, osteoporosis, muscle weakness with gait abnormalities, polymyalgia rheumatica
<b>Integumentary</b>	Atrophy of sebaceous and sweat glands Decreased epidermal and dermal thickness, dermal vascularity, melanocytes, collagen synthesis	Increased lentigo, cherry hemangiomas, pruritus, seborrheic keratosis, herpes zoster, decubitus ulcers, skin cancer
<b>Psychiatry</b>	None	Increased depression, dementia, delirium, suicidality, substance abuse, anxiety, insomnia



### Most Common Acute Disorders in the Elderly

- Cardiovascular disease (CHF, CVA, MI)
- Fracture (hip, vertebrae, wrist)
- Medication-related
- Pneumonia
- Sepsis



### Most Common Chronic Disorders in the Elderly

- Arthritis
- Cataracts and other visual problems
- COPD
- Cardiovascular disease
- Diabetes Mellitus (Type 2)
- Hearing impairment
- Hypertension
- Mental disorders
- Orthopedic disorders
- Sinusitis



# Differential Diagnoses of Common Presentations

## Constipation

- see [Gastroenterology](#), G24

### Definition

- less than 3 bowel movements in one week and/or hard stools, straining, sense of blockade, needing manual maneuvers or incomplete evacuation on more than 25% of occasions for at least 12 wk (does not need to be consecutive)

### Epidemiology

- chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation)

### Pathophysiology

- impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
- colorectal dysmotility

### Treatment

- non-pharmacological
  - increase fibre intake
  - ensure adequate fluid intake
  - discourage chronic laxative use
  - engage in regular exercise
  - review medication regime, reduce dosages or substitute
- pharmacologic
  - see *Common Medications*, GM15



### Risk Factors for Constipation in the Elderly Include:

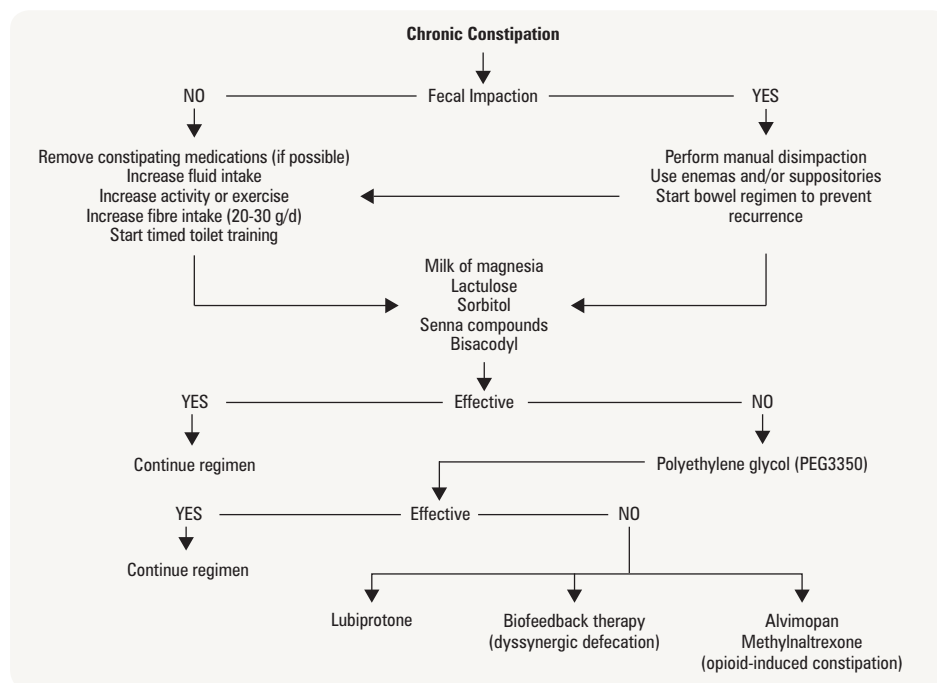
- Immobility
- Diet: low fibre/calorie diet, dehydration
- Medications:
  - Polypharmacy
  - Drugs: narcotics, calcium channel blockers, anticholinergics
- GI: obstructive lesions (bowel obstruction, cancer, diverticular disease, IBD, strictures, uterine prolapse), altered colonic motility (IBS, colonic inertia)
- Neurological: spinal cord injury, Parkinson's disease, stroke, autonomic dysfunction
- Metabolic: diabetes, hypokalemia, hypercalcemia
- Psychiatric: depression, dementia



Remember to first exclude low fibre and lack of activity as causes of constipation.



Docusate sodium has been shown to be ineffective for the prevention/ treatment of constipation in the elderly.



**Figure 1. Treatment algorithm for the management of chronic constipation in the elderly**

Adapted from: Clin Interv Aging 2010;5:163-171

## Delirium, Dementia and Depression

- see [Psychiatry](#), PS19, PS20, PS9 and [Neurology](#), N17

### Definition

- pathologic decrease in memory, language, or executive function

### Differential Diagnosis

- delirium, dementia, or pseudodementia of depression



Table 3. Differentiating the Three Ds of Cognitive Impairment

	Dementia	Delirium	Depression
<b>Onset</b>	Gradual or step-wise decline	Acute (hours-days)	Subacute
<b>Duration</b>	Months-years	Days-weeks	Variable
<b>Natural History</b>	Progressive, usually irreversible	Fluctuating, reversible High morbidity/mortality in very old	Recurrent Usually reversible
<b>Level of Consciousness</b>	Normal	Fluctuating	Normal
<b>Attention</b>	Intact initially	Decreased, wandering	Difficulty concentrating
<b>Orientation</b>	Intact initially	Impaired, fluctuates	Intact
<b>Behaviour</b>	Disinhibition, loss of ADL/IADLs, personality change	Severe agitation/retardation	Importuning, self-harm/suicide
<b>Psychomotor</b>	Normal	Fluctuates between extremes	Slowing
<b>Sleep-Wake Cycle</b>	Fragmented sleep at night	Reversed sleep-wake cycle	Early morning awakening
<b>Mood and Affect</b>	Labile but not usually anxious	Anxious, irritable, fluctuating	Depressed, stable
<b>Cognition</b>	Decreased executive function, paucity of thought	Fluctuation preceded by mood changes	Concentration impaired
<b>Memory Loss</b>	Recent, eventually remote	Marked recent	Recent
<b>Language</b>	Agnosia, aphasia, decreased comprehension, repetition	Dysnomia, dysgraphia, speech rambling, subject changes, incoherence	Not affected
<b>Delusions</b>	Compensatory	Nightmarish, poorly formed	Nihilistic, somatic
<b>Hallucinations</b>	Variable, Vacuous, bland	Visual common, frightening/bizarre	Self-deprecatory

### Delirium Prevention in Elderly

- ensure optimal vision and hearing to support orientation (e.g. clean, appropriate eyewear and hearing aids)
- provide adequate nutrition and hydration (up in chair to eat and drink whenever feasible)
- encourage regular mobilization to build and maintain strength, balance and endurance
- avoid unnecessary medications and monitor for drug interactions
- avoid bladder catheterization if possible
- ensure adequate sleep



#### Antipsychotics for Delirium

Cochrane DB Syst Rev 2009;CD005594

**Objectives:** To compare the efficacy and incidence of adverse effects of haloperidol with risperidone, olanzapine and quetiapine in the treatment of delirium.

**Selection Criteria:** Types of studies included unconfounded, randomized trials with concealed allocation of subjects.

**Results:** Three studies were included, comparing haloperidol with risperidone, olanzapine and placebo in the management of delirium and in the incidence of adverse drug reactions. Decreases in delirium scores were not significantly different when comparing the effect of low dose haloperidol (<3.0 mg/d) with olanzapine and risperidone (odds ratio 0.63; 95% CI 0.29 to 1.38; p=0.25). High dose haloperidol (>4.5 mg/d) was associated with an increased incidence of extrapyramidal adverse effects compared with olanzapine. Low dose haloperidol decreased the severity and duration of delirium in post-operative patients, although not the incidence of delirium compared to placebo.

**Author's Conclusions:** There is no evidence that haloperidol in low dosage has different efficacy in comparison with the atypical antipsychotics olanzapine and risperidone in the management of delirium or has a greater frequency of adverse drug effects than these drugs. High dose haloperidol was associated with a greater incidence of side effects. Low dose haloperidol may be effective in decreasing the degree and duration of delirium in post-operative patients, compared with placebo. However, all studies were small and should be repeated.

## Elder Abuse

### Definition

- includes physical abuse, sexual abuse, emotional/psychological abuse, financial abuse, abandonment and neglect
- elder abuse is a criminal offence under the Criminal Code of Canada
- in the U.S., most states have criminal penalties for elder abuse

### Epidemiology

- in Canada, approximately 4% of elderly persons living in private homes have suffered abuse
- in the U.S., estimates of the frequency of elder abuse range from 3-8%
- physician reporting is mandatory only in Newfoundland, Nova Scotia and Prince Edward Island; in Ontario, only abuse occurring in nursing homes is mandatory to report
- insufficient evidence to include/exclude screening in the Periodic Health Exam

### Risk Factors

Table 4. Risk Factors for Elder Abuse

<b>Situational Factors</b>	Isolation Unstable or unsafe living arrangements Lack of family, community or living facility resources for additional care
<b>Victim Characteristics</b>	Physical or emotional dependence on caregiver Lack of close family ties History of family violence Dementia or recent deterioration in health
<b>Perpetrator Characteristics</b>	Related to victim Living with victim Long duration of care for victim (mean 9.5 yr) Financial, marital, occupational or other stressors

## Caregiver Abuse Screen (CASE)

- instructions:
  - to be answered by caregivers, if answer “yes” to a question, further explore issue
  - the more “yes” responses, the more likely the presence of abuse
- screening tool
  - please answer the following questions as a helper/caregiver:
    1. Do you sometimes have trouble making \_\_\_\_\_ control his/her temper or aggression?
    2. Do you often feel you are being forced to act out of character/do things you feel badly about?
    3. Do you find it difficult to manage \_\_\_\_\_’s behavior?
    4. Do you sometimes feel that you are forced to be rough with \_\_\_\_\_?
    5. Do you sometimes feel that you can’t do what is really necessary or what should be done for \_\_\_\_\_?
    6. Do you often feel you have to reject/ignore \_\_\_\_\_?
    7. Do you often feel so tired and exhausted that you cannot meet \_\_\_\_\_’s needs?
    8. Do you often feel you have to yell at \_\_\_\_\_?

From: NICE. Case: Caregiver Abuse Screen. 2010. Reproduced with permission from NICE.

## Management

- assess safety and determine capacity to make decisions about living arrangements
- establish need for hospitalization or alternate accommodation (e.g. immediate risk of physical harm by self or caregiver)
- involve multidisciplinary team (e.g. nurse, social worker, family members and physicians including geriatrician, psychiatrist or family physician)
- educate and assist caregiver, contact local resources (e.g. legal aid, crisis support, PSW, caregiver support groups)
- interpret critical and lab findings that are key in exclusion, differentiation and diagnosis

## Falls

### Epidemiology

- 30-40% of people >65 yr old and ~50% of people >80 yr old fall each year
  - equally common between men and women, but more likely to result in injury in women
  - 5% of falls lead to hospitalization
  - 5-10% associated with serious injuries (e.g. hip fracture, head injury, laceration)
    - ♦ 1-2% of falls associated with hip fracture
    - ♦ 15% die in hospital, 33% 1-yr mortality
  - between 25-75% do not recover to previous level of ADL function
  - mortality increases with age (171/100,000 in men >85 yr old) and type of injury (25% with hip fracture die within 6 mo)

### Etiology

- multifactorial
- extrinsic
  - environmental (e.g. home layout, lighting, stairs, footwear), accidental, abuse
  - medications/substances (e.g. alcohol)
  - within one month of hospital discharge, acute illness, exacerbation of chronic illness
- intrinsic
  - orthostatic/syncopal
  - age-related changes and diseases associated with aging: musculoskeletal (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), metabolic (glucose, electrolytes)
  - past history of a fall

### Investigations

- directed by history and physical
- comprehensive geriatric assessment to identify all potential causes
- CBC, electrolytes, BUN, creatinine, glucose,  $\text{Ca}^{2+}$ , TSH,  $\text{B}_{12}$ , urinalysis, cardiac enzymes, ECG, CT head

### Prevention

- multidisciplinary, multifactorial, health and environment risk factor screening and intervention programs in the community
- muscle strengthening, balance retraining and group exercise programs (e.g. tai chi)
- home hazard assessment and modification (e.g. remove rugs, add shower bars, etc.)
- prescription of vitamin D 1000 IU daily
- tapering or gradual discontinuation of psychotropic medication
- postural hypotension, heart rate, and rhythm abnormalities management
- eyesight and footwear optimization



### Red Flags for Elder Abuse

- Delay in seeking medical attention
- Disparity in histories
- Implausible or vague explanations
- Frequent emergency room visits for exacerbations of chronic disease despite plan for medical care and adequate resources
- Presentation of functionally impaired patient without designated caregiver
- Lab findings inconsistent with history



### Medication as a Risk Factor for Falls: Critical Systematic Review

*J Gerontol A Biol Sci Med Sci* 2007;62:1172-1181

**Purpose:** To review all original articles systematically examining medication use as a risk factor for falls or fall-related fractures in people 60 yr and older.

**Study Selection:** Studies investigating “falls” or “accidental falls” and “pharmaceutical preparations” or specific groups of drugs were included. Studies not meeting the age criterion, not controlled with nonusers of target medicines or nonfallers, or with no clear definition of target medication were excluded.

**Results:** 28 observational studies and one randomized controlled trial met the inclusion criteria. The outcome measure was fall in 22 studies and fracture in 7 studies. The main group of drugs associated with an increased risk of falling was psychotropics: benzodiazepines, antidepressants and antipsychotics. Antiepileptics and drugs that lower blood pressure were weakly associated with falls.

**Conclusions:** Central nervous system drugs, especially psychotropics, seem to be associated with an increased risk of falls. Further studies are required due to lack of clear definition of a fall, target medications or prospective follow-up.



### Key Physical Findings in the Elderly Patient Who Falls or Nearly Falls

#### I HATE FALLING

Inflammation of joints

Hypotension (orthostatic changes)

Auditory and visual abnormalities

Tremor

Equilibrium (balance) problem

Foot Problems

Arrhythmia, heart block or valvular disease

Leg-length discrepancy

Lack of conditioning (generalized weakness)

Illness

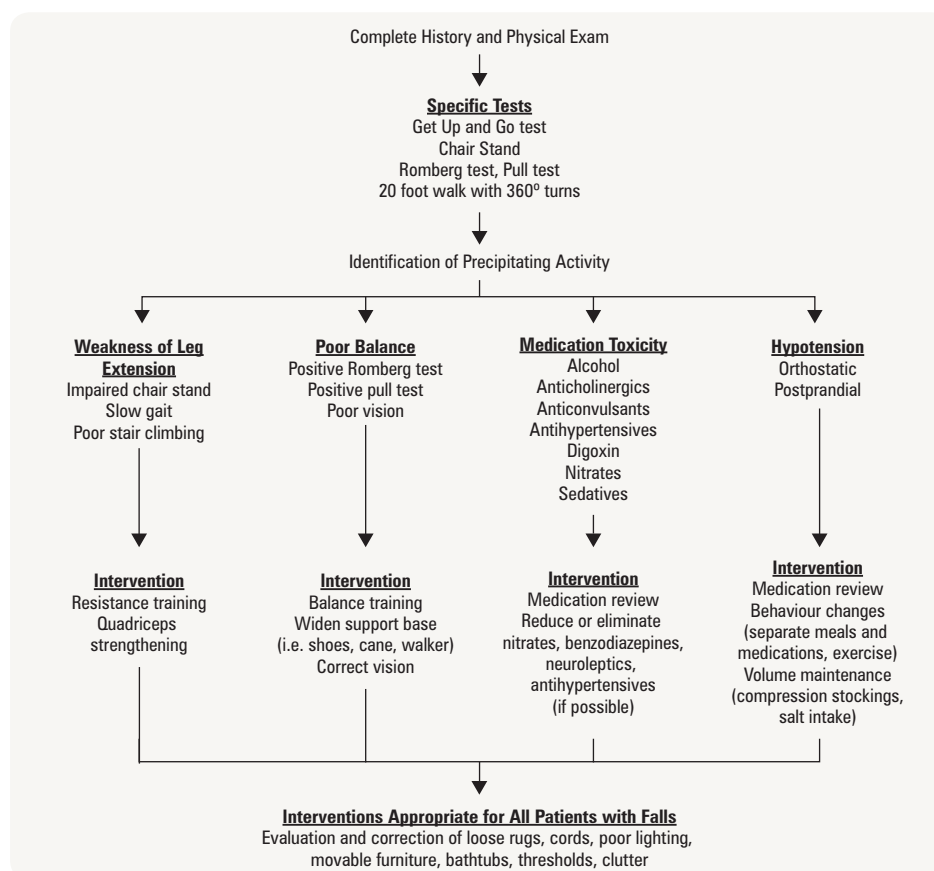
Nutrition

Gait disturbance

*Am Fam Phys* 2001;61:2159-2172



A history of falls within the past 1-2 yr is a predictor of motor vehicle crashes in the older population. These patients should be evaluated on their ability to drive and counseled about driving.



**Figure 2. Approach to falls in the elderly**

Adapted from: JAMA 2007;297:77-86 and NEJM 1994;331:821-827



#### Drugs That May Increase the Risk of Falling

- Sedative-hypnotic and anxiolytic drugs (especially long-acting benzodiazepines)
- Antidepressants (including MAOIs, SSRIs, TCAs)
- Antipsychotics and tranquilizers (phenothiazines and butyrophenones)
- Antihypertensive drugs
- Antiarrhythmics (Class IA)
- Diuretics
- Systemic corticosteroids
- NSAIDs
- Anticholinergic drugs
- Hypoglycemic agents
- Alcohol

Adapted from: Am Fam Phys 2001;61:2159-2172  
Geriatrics At Your Fingertips, 13th ed. New York: Am Geriat Soc, 2011



#### Fall Prevention Tips

- Improve lighting, especially on stairs
- Caution while adjusting to new bifocal prescription (poor depth perception)
- Siderails in bathtubs
- Railings on steps
- Connect patient to lifeline button signaling systems
- Remove loose mats or carpets, telephone cords and other tripping hazards
- Recommend support hose for varicose veins and swelling of ankles

Essential Geriatrics: Managing 6 Conditions. Patient Care Canada 1997;8



#### Will My Patient Fall?

JAMA 2007;297:77-86

**Purpose:** To identify the prognostic value of risk factors for future falls among older patients.

**Study Selection:** Prospective cohort studies of risk factors for falls that performed a multivariate analysis of such factors.

**Results:** 18 studies were included. Clinically identifiable risk factors were identified across 6 domains: orthostatic hypotension, visual impairment, impairment of gait or balance, medication use, limitations in basic or instrumental activities of daily living and cognitive impairment. The estimated pretest probability of falling at least once in any given yr for individuals 65 yr and older was 27% (95% CI, 19%-36%). Patients who have fallen in the past yr are more likely to fall again (LR2.3-2.8). The most consistent predictors of future falls are clinically detected abnormalities of gait or balance (LR 1.7-2.4). Visual impairment, medication variables, decreased activities of daily living and impaired cognition did not consistently predict falls across studies. Orthostatic hypotension did not predict falls after controlling for other factors.

**Conclusions:** Screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past yr. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problem are at higher risk of future falls.

## Frailty (Failure to Thrive)

### Definition

- declining independence and functional capacity with loss of energy, vigor and/or weight in older adults
- not an inevitable consequence of aging

### Etiology

- malnutrition, functional impairment, cognitive impairment and depression

**Table 5. Common Medical Conditions Associated with Failure to Thrive**

Medical Condition	Cause of Failure to Thrive
Cancer	Metastases, malnutrition, cachexia
Chronic lung disease	Respiratory failure
Chronic renal insufficiency	Renal failure
Chronic steroid use	Steroid myopathy, diabetes, osteoporosis, vision loss
Cirrhosis, hepatitis	Hepatic failure
Depression, other psychiatric disorder	Major depression, psychosis, poor functional status, cognitive loss
Diabetes	Malabsorption, poor glucose homeostasis, end-organ damage
Gastrointestinal surgery	Malabsorption, malnutrition
Hip, long bone fracture	Functional impairment
Inflammatory bowel disease	Malabsorption, malnutrition
Myocardial infarction, congestive heart failure	Cardiac failure
Recurrent UTI, pneumonia	Chronic infection, functional impairment
Rheumatologic disease (GCA, RA, SLE)	Chronic inflammation
Stroke	Dysphagia, depression, cognitive loss, functional impairment
Tuberculosis, other systemic infection	Chronic infection

Source: Clin Geriatr Med 1997;13:769-778

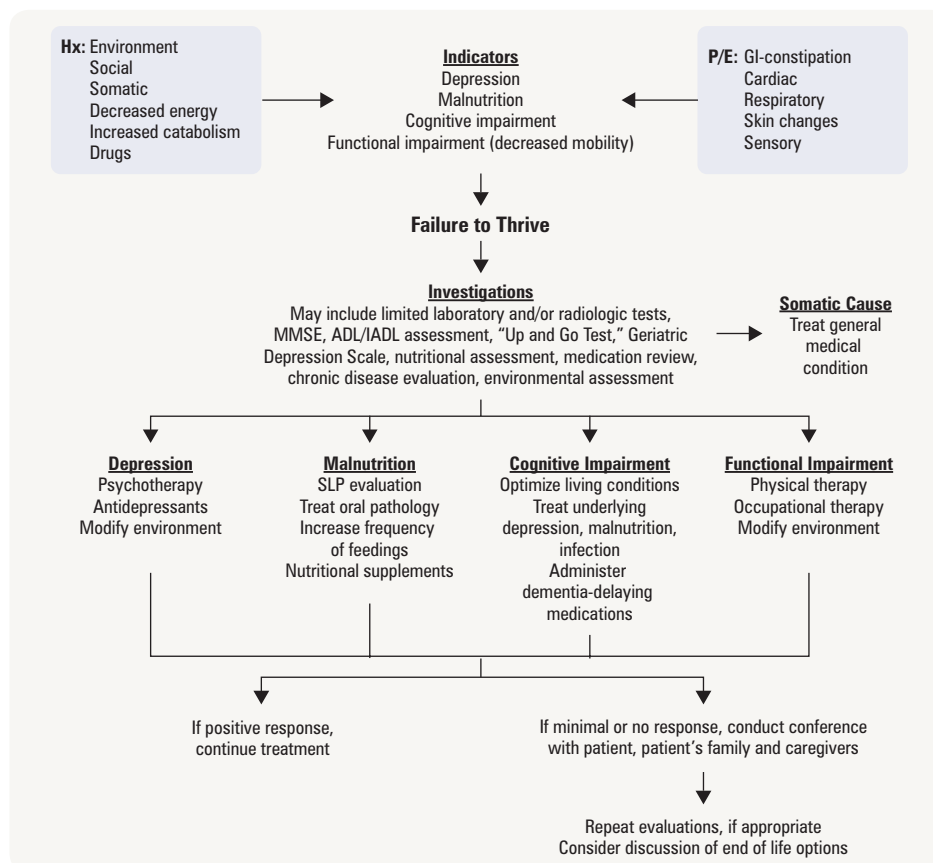


Figure 3. Evaluation of the geriatric patient who is failing in the community

Adapted from: Ann Intern Med 1996;24:1072-1078



#### Four Syndromes in Failure to Thrive

##### My Pa Can't Drive

Malnutrition  
Physical impairment  
Cognitive impairment  
Depression



#### A Global Clinical Measure of Fitness and Frailty in Elderly People

CMAJ 2005;173:489-495

**Purpose:** To develop a tool to define clinical frailty.

**Methods:** A five yr prospective cohort study with 2305 participants in the Canadian Study of Health and Aging (CSHA-2). A 7-point Clinical Frailty Scale was developed and assessed for its ability to predict death and need for institutionalization. It was also compared to other established tools (i.e. Frailty Index).

**Results:** The CSHA Clinical Frailty Scale had 7 points ranging from 'Very Fit' (robust, active, energetic) to 'Severely Frail' (completely dependent, terminally ill). Each 1-category increment increased medium-term risk of death by 21% (95%CI 12.5%-30.6%) and entry into institutional care by 23.9% (95%CI 8.8%-41.2%). It correlated well with the Frailty Index ( $r=0.8$ ) and was better than measures of cognition, function or co-morbidity in assessing risk for death.

**Conclusions:** The CSHA Clinical Frailty Scale is predictive of death and need for an institution.



#### Functional Assessment (ADLs and IADLs)

##### ADLs: ABCDE-TT

Ambling  
Bathing  
Continence  
Dressing  
Eating  
Transferring  
Toileting

##### IADLs: SHAFT-TT

Shopping  
Housework  
Accounting/Managing finances  
Food preparation  
Transportation  
Telephone  
Taking medications

Can use formal assessment tools such as the Lawton-Brody Instrumental Activities of Daily Living Scale to assess functioning.



#### Transient Causes of Incontinence

##### DIAPERS

Delirium  
Infection  
Atrophic urethritis/vaginitis  
Pharmaceuticals  
Excessive urine output  
Restricted mobility  
Stool impaction

## Incontinence

### FECAL INCONTINENCE

#### Epidemiology

- second leading cause of nursing home placement

#### Etiology

- commonly multifactorial
  - structural abnormalities
  - trauma (e.g. prior vaginal delivery, surgery)
  - prolapse
  - tumour/trauma (e.g. brain, spinal cord, cauda equina)
  - overflow (e.g. encopresis, impaction)
- functional abnormalities
  - neurologic conditions – neuropathy, multiple sclerosis, stroke, dementia
- others
  - constipation with overflow may be a factor
  - psychosis (willful soiling)
  - age >80 yr: decreased external sphincter strength and weak anal squeeze, increased rectal compliance, decreased resting tone and internal sphincter, impaired anal sensation
  - medications (e.g. laxatives, anticholinergics, antidepressants, caffeine, muscle relaxants)

#### Investigations (if cause not apparent from history and physical)

- differentiate true incontinence from frequency and urgency (i.e. IBS, IBD)
- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

#### Management

- diet/bulking agent if stool is liquid or loose
- disimpaction, prevent impaction
- anti-diarrheal agents (e.g. loperamide)
- regular defecation program in patients with dementia
- counsel about biofeedback therapy (retraining of pelvic floor muscles)



## URINARY INCONTINENCE

- see [Urology](#), U6

### Epidemiology

- 15-30% prevalence dwelling in community and at least 50% of institutionalized seniors
- morbidity: cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality

### Pathophysiology

- not a normal part of aging, urinary incontinence is a loss of control due to a combination of:
  - genitourinary pathology: increased post-void residual volume, increased involuntary bladder contractions (urge incontinence)
  - age-related changes: decreased bladder capacity
  - comorbid conditions and medications
  - functional impairment
- in elderly women: decline in bladder outlet and urethral resistance pressure promoting stress incontinence
- in elderly men: prostatic enlargement can cause overflow and urge incontinence



## Gait Disorders

- see [Neurology](#), N29

## Hazards of Hospitalization

**Table 6. Recommendations for Sequelae of Hospitalization in Older Patients**

Sequelae	Recommendations
Malnutrition	No dietary restrictions (except diabetes), assistance, dentures if necessary, sitting in a chair to eat
Urinary incontinence	Medication review, remove environmental barriers, discontinue use of catheter
Depression	Routine screening
Adverse drug event	Medication review
Confusion/delirium	Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints
Pressure ulcers	Low-resistance mattress, daily inspection, repositioning every 2 h
Infection	Early mobilization, remove unnecessary IV lines, catheters, NG tubes
Falls	Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review
Hypotension/dehydration	Early recognition and repletion
Diminished aerobic capacity/loss of muscle strength/contractures	Early mobilization
Decreased respiratory function	Incentive spirometry, physiotherapy



### Cognitive Decline after Hospitalization in a Community Population of Older Persons

*Neurology* 2012;78:950-956

**Study:** 12-yr Cohort study of 1870 elderly residents interviewed at 3-yr intervals with cognitive testing and information on hospitalization (from hospital records).

**Results:** 71.4% of residents were hospitalized at least once. Post-hospital cognitive decline measured by episodic memory (3.3-fold increase) and executive function (1.7-fold increase) was evident and not related to cognitive function at baseline but moderately correlated with rate of cognitive decline before hospitalization ( $r=0.55$ ).

**Conclusions:** Cognitive function declines post-hospitalization even after controlling for illness severity and pre-hospital cognitive decline.



### Treatment of Hypertension in Patients 80 Years of Age or Older

*NEJM* 2008;358:1887-1898

**Study:** Randomized, double-blind, placebo-controlled, multicentre trial.

**Subjects:** 3845 patients who were 80 yr of age or older and had a sustained systolic blood pressure of 160 mmHg were followed for a median 1.8 yr.

**Intervention:** Indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mmHg.

**Primary Outcome:** Fatal or nonfatal stroke.

**Results:** Mean BP was 173.0/90.8 mmHg. At 2 yr, the mean BP while sitting was 15.0/6.1 mmHg lower in the treatment group than in the placebo group. Treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% CI, -1 to 51;  $p=0.06$ ), 39% reduction in the rate of death from stroke (95% CI, 1 to 62;  $p=0.05$ ), 21% reduction in the rate of death from any cause (95% CI, 4 to 35;  $p=0.02$ ), 23% reduction in the rate of death from cardiovascular causes (95% CI, -1 to 40;  $p=0.06$ ), and 64% reduction in the rate of heart failure (95% CI, 42 to 78;  $p<0.001$ ). Fewer serious adverse events were reported in the treatment group (358 vs. 448 in the placebo group;  $p=0.001$ ).

**Conclusions:** Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 yr of age or older reduces death from stroke, death from any cause and the incidence of heart failure.

## Hypertension

- see [Family Medicine](#), FM37
- 60-80% of elderly (>65 yr old) have hypertension
  - 60% of these have isolated systolic HTN
  - the benefit of treating hypertension in the elderly is 2-4 times greater than that achieved in the treatment of younger patients with primary hypertension
  - systolic and pulse pressure are major predictors of outcome in the elderly patient
  - in older adults, base treatment on sBP
- target BP: sBP <140, 65<dBP<90; for patients with DM: sBP <130, dBP <80
  - not recommended to lower BP below 120/80
- treatment:
  - non-pharmacologic treatments are first-line, then thiazide monotherapy is recommended
  - add ACEI/ARB if also atherosclerosis, DM, CHF or chronic kidney disease
  - add  $\beta$ -blockers if also angina or CHF



## Immobility

### Complications

- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- musculoskeletal: atrophy, contractures, bone loss
- skin: pressure ulcers
- psychological: sensory deprivation, delirium, depression

## Immunizations

- the following immunizations are recommended for people 65 yr of age and older
  - tetanus: every 10 yr
  - pneumococcus: every 5 yr
  - influenza: every autumn
  - herpes zoster: Zostivax®

## Malnutrition

### Definition

- involuntary weight loss of  $\geq 5\%$  baseline body weight or  $\geq 5$  kg
- hypoalbuminemia, hypocholesterolemia

### Etiology

- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals or feeding oneself due to functional impairment)
- stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical: dental problems, dysphagia
- age-related changes: appetite dysregulation, decreased thirst
- mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

### Clinical Features

- history
  - recent or chronic illness
    - ♦ depression, GI symptoms
  - functional disability: impaired ADLs and IADLs
  - social factors: economic barriers, dental problems and living situation (e.g. living alone)
  - constitutional symptoms e.g. recent weight loss
- physical examination
  - BMI  $< 23.5$  in males,  $< 22$  in females should raise concern
  - temporal wasting, muscle wasting, presence of triceps skin fold
  - assess cognition

### Investigations

- CBC, electrolytes,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{PO}_4^{3-}$ , creatinine, LFTs (albumin, INR, bilirubin),  $\text{B}_{12}$ , folate, TSH, transferrin, lipid profile, urinalysis, ESR, CXR

## Osteoporosis

- see [Endocrinology](#), E42

## Presbycusis

- see [Otolaryngology](#), OT19



#### Remember to calculate BMI

BMI outside 22-27 kg/m<sup>2</sup> is a health risk.



#### Calculating Basic Caloric and Fluid Requirements

WHO daily energy estimates for adults  $> 60$  yr:

Female:  $10.5 \times (\text{weight in kg}) + 596$

Male:  $13.5 \times (\text{weight in kg}) + 487$

Maintenance fluid requirements for the elderly without cardiac or renal disease: 1500-2500 cc/24 h.



#### Etiology of Malnutrition in the Elderly

##### MEALS ON WHEELS

##### Medications

Emotional problems

Anorexia

Late-life paranoia

Swallowing disorders

Oral problems

Nosocomial infections

Wandering/dementia related activity

Hyperthyroid/Hypercalcemia/

Hypoadrenalism

Enteric disorders

Eating problems

Low-salt/Low-fat diet

Stones



## Pressure Ulcers

- see [Plastic Surgery](#), PL16

### Risk Factors

- extrinsic factors: friction, pressure, shear force
- intrinsic factors: immobility, malnutrition, moisture, sensory loss

**Table 7. Classification of Pressure Ulcers**

<b>Stage I</b>	Changes include skin temperature, tissue consistency or sensation An area of persistent erythema in lightly pigmented, intact skin; in darker skin, it may appear red, blue or purple
<b>Stage II</b>	Partial thickness skin loss involving the epidermis, dermis or both The ulcer is superficial and presents as an abrasion, blister or shallow crater
<b>Stage III</b>	Full thickness skin loss involving damage or necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia Presents as a deep crater with or without undermining of adjacent tissue
<b>Stage IV</b>	Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures May have associated undermining and/or sinus tracts

### Prevention

- pressure reduction
  - frequent repositioning
  - pressure-reducing devices (static, dynamic)
- maintaining nutrition, encouraging mobility and managing incontinence

### Treatment

- optimize nutritional status
- minimize pressure on wound
- analgesia
- wound debridement (mechanical, enzymatic, autolytic) and dressing application
- maintain moist wound environment to enable re-epithelialization
- treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
- swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
- stage IV ulcers typically warrant surgical debridement
- consider other treatment options
  - negative pressure wound therapy/vacuum-assisted closure (VAC)
  - biological agents: application of fibroblast growth factor, platelet-derived growth factor to wound
  - non-contact normothermic wound therapy
  - electrotherapy



#### Pressure-reducing Devices

Static devices distribute pressure over a greater surface area. Dynamic devices use alternating air currents to shift pressure to different body sites.

## Driving Competency



### Reporting Requirements

- physician-reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia and Alberta, where it is discretionary
- not an issue unique to geriatrics – any patient may suffer from a medical condition that impairs their ability to drive should be reported
- in the U.S., varies by state

### Conditions that may Impair Driving

**Table 8. Conditions that Impair Driving**

<b>Alcohol</b>	Patients with history of impaired driving and those with high probability of future impaired driving should not drive until further assessed Alcohol dependence or abuse: if suspected, should be advised not to drive Alcohol withdrawal seizure: must complete a rehabilitation program and remain abstinent and seizure-free for 6 mo before driving
<b>Blood Pressure Abnormalities</b>	Hypertension: sustained BP >170/110 should be evaluated carefully Hypotension: if syncopal, discontinue until attacks are treated and preventable

**Table 8. Conditions that Impair Driving** (continued)

<b>Cardiovascular Disease</b>	Suspected asymptomatic CAD or stable angina: no restrictions STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for one month following hospital discharge NSTEMI with minor LV damage, unstable angina: no driving for 48 h if percutaneous coronary intervention (PCI) performed or 7 d if no PCI performed
<b>Cerebrovascular Conditions</b>	TIA: should not be allowed to drive until a medical assessment is completed Stroke: should not drive for at least one month; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure
<b>COPD</b>	Mild/moderate impairment: no restrictions Moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen
<b>Cognitive Impairment/Dementia</b>	Moderate to severe dementia is a contraindication to driving; defined as the "inability to independently perform 2 or more IADLs or any basic ADL" Patients with mild dementia should be assessed; if indicated, refer to specialized driving testing centre; if deemed fit to drive, re-evaluate patient every 6-12 mo Poor performance on MMSE, clock drawing or Trails B suggests a need to investigate driving ability further MMSE score alone (whether normal or low) is insufficient to determine fitness to drive
<b>Diabetes</b>	Diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular or cerebrovascular disease) Insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 mo
<b>Drugs</b>	Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants Degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving
<b>Hearing Loss</b>	Effect of impaired hearing on ability to drive safely is controversial Acute labyrinthitis, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves
<b>Musculoskeletal Disorders</b>	Physician's role is to report etiology, prognosis and extent of disability (pain, range of motion, coordination, muscle strength)
<b>Post-operative</b>	Outpatient, conscious sedation: no driving for 24 h Outpatient, general anesthesia: no driving for $\geq 24$ h
<b>Seizures</b>	First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head Epilepsy: can drive if seizure-free on medication and physician has insight into patient compliance
<b>Sleep Disorders</b>	If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive
<b>Visual Impairment</b>	Visual acuity: contraindicated to drive if $< 20/50$ with both eyes examined simultaneously Visual field: contraindicated to drive if $< 120^\circ$ along horizontal meridian and $15^\circ$ continuous above and below fixation with both eyes examined simultaneously

N.B. guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving



#### Systematic Review of Driving Risk and the Efficacy of Compensatory Strategies in Persons with Dementia

*J Am Geriatr Soc* 2007;55:878-884

**Purpose:** To determine whether persons with dementia are at greater driving risk and, if so, to estimate the magnitude of this risk and determine whether there are efficacious methods to compensate for or accommodate it.

**Study Selection:** Systematic review of the case-control studies of drivers with a diagnosis of dementia.

**Results:** Drivers with dementia universally exhibited poorer performance on road tests and simulator evaluations. The one study that used an objective measure of motor vehicle crashes found that the crash risk in persons with dementia was 2 to 2.5 times greater than matched controls. No studies were found that examined the efficacy of methods to compensate for or accommodate the decreased driving performance.

**Conclusions:** Drivers with dementia are poorer drivers than cognitively normal drivers, but studies have not consistently demonstrated higher crash rates. Clinicians and policy makers must take these findings into account when addressing issues pertinent to drivers with a diagnosis of dementia.



#### Key Factors to Consider in Older Drivers

##### SAFEDRIVE

Safety record

Attention (e.g. concentration lapses, episodes of disorientation)

Family observations

Ethanol abuse

Drugs

Reaction time

Intellectual impairment

Vision/Visuospatial function

Executive functions (e.g. planning, decision-making, self-monitoring behaviours)

*Geriatrics* 1996;51:36-45

## Health Care Institutions

**Table 9. Classification of Health Care Services and Institutions**

Institution/Service	Description
<b>Community Support Services</b>	Health care services offered at home for those who can live independently at home or under the care of family members including professional health care services, personal care and support (ADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks, etc.)
<b>Residential</b>	Divided into short ( $< 60$ -90 d/yr) and long (indefinite) stay
a) <b>Seniors Affordable Housing</b>	Seniors who live independently and manage their own care but prefer to live near other seniors; usually has accessibility features and rent is adjusted based on income
b) <b>Retirement/Nursing Home</b>	Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned
c) <b>Supportive Housing</b>	Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment and may offer some physiotherapy and rehabilitation services
d) <b>Long-term Care/Skilled Nursing Facility</b>	Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital
e) <b>Hospice</b>	Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis $\leq 3$ mo

- names of community health care institutions, types of facilities and services offered vary between geographical locations
- factors to consider when seeking services/institutions include level of care required, support networks, duration of stay and cost

## Palliative and End-of-Life Care



### Principles and Quality of Life

- support, educate and treat both patient and family
- address physical, psychological, social and spiritual needs
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

### End-of-Life Care Discussions

#### When to Initiate End-of-Life Care Discussions

- recent hospitalization for serious illness
- severe progressive medical condition(s)
- death expected within 6-12 mo
- patient inquires about end-of-life care

#### Suggested Topics for Discussion

- goals of care (disease vs. symptom management)
- advance directives, power of attorney, public guardian and trustee
- treatment options and likelihood of success
- common medical interventions
  - mechanical ventilation
  - antibiotic therapy
  - feeding tubes
- resuscitation options and likelihood of success (Full Code vs. DNR status including preferences for CPR, intubation, ICU admission, artificial hydration)

### Power of Attorney

- see [Ethical, Legal and Organizational Aspects of Medicine](#), ELOAM8



### Instructional Advance Directives

- see [Ethical, Legal and Organizational Aspects of Medicine](#), ELOAM8



### Symptom Management

#### Assessment Tools

- **Edmonton Symptom Assessment System (ESAS):** a tool that asks patients to rate the intensity of symptoms from 0 to 10 and allows for tracking of the efficacy of interventions. Assesses: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well being, shortness of breath, and "other problem"
- **Palliative Performance Scale (PPS):** a tool that uses functional status to predict survival in terminally ill patients. Assesses 5 components: ambulation, activity and evidence of disease, self-care, intake and conscious level

Source: Journal of Palliative Care, 1991;7:6-9 and Palliative Performance Scale, Victoria Hospice Society, 2006;120-121

Table 10. Management of Common End-of-Life Symptoms

Symptom	Non-Pharmacologic Management	Pharmacologic Management
<b>Constipation</b>	Rule out obstruction, impaction, anorectal disease; hydration and high fibre intake; increase mobility	Stop unnecessary opioids and medications with anticholinergic side effects; provide stool softener (e.g. docusate sodium), increase peristalsis (e.g. senna), alter water and electrolyte secretion (e.g. magnesium hydroxide)
<b>Death Rattle/ Increased Pulmonary Secretions</b>	Oral suctioning Discontinue unnecessary IV solutions	Scopolamine SC or transdermal
<b>Dry mouth</b>	Oral hygiene q2h, ice cubes, sugarless gum	Artificial saliva substitutes, bethanechol, pilocarpine 1% solution as mouth rinse
<b>Dysphagia</b>	Frequent small feeds, ideally seated, keep head of bed elevated for 30 min after eating, suction as necessary	Treat painful mucositis (diphenhydramine: lidocaine: Maalox® in a 1:2:8 mixture), candidiasis (fluconazole) as necessary
<b>Dyspnea</b>	Elevate head of bed, eliminate allergens, open window/use fan	Oxygen, bronchodilators, opioids (e.g. morphine, hydromorphone)
<b>Hiccups</b>	Dry sugar, breathing in paper bag	Chlorpromazine, haloperidol, metoclopramide, baclofen, marijuana
<b>Nausea and Vomiting</b>	Frequent and small meals, avoid offensive strong odours, treat constipation if present	Raised ICP: dexamethasone Anticipatory nausea, anxiety: lorazepam Vestibular disease, vertigo: dimenhydrinate Drug induced, hepatic or renal failure: prochlorperazine, haloperidol GERD: PPI or H2 antagonist Gastric stasis: metoclopramide Bowel obstruction: metoclopramide, dexamethasone, octreotide
<b>Pain</b>	Hot and cold compresses, music therapy, relaxation techniques, individualized program of physical activity designed to improve flexibility, strength and endurance	Nociceptive pain: non-opioids (NSAIDs, acetaminophen), weak opioids (codeine, hydrocodone, oxycodone), strong opioids (morphine, hydromorphone, oxycodone, fentanyl) Neuropathic pain: anticonvulsants (gabapentin, pregabalin), antidepressants (TCAs, SSRIs), steroids (dexamethasone) Bony pain: non-opioids, weak opioids, bisphosphonates, radiation therapy
<b>Pruritus</b>	Bathing with tepid water, avoid soap, bath oils; sodium bicarbonate for jaundice	Antihistamines, phenothiazines, topical corticosteroids, calamine lotion
<b>Weakness</b>	Modify environment and activities to decrease energy expenditure	Treat insomnia, anemia, depression; consider psychostimulants

Source: J Am Geriatr Soc 2002;50:S205-S224 and On Continuing Practice 1993;20:20-25

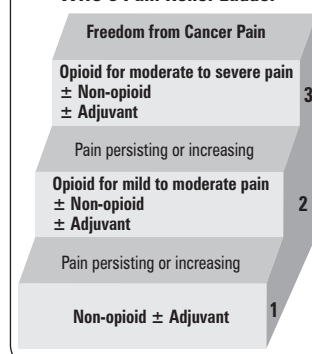
## Geriatric Pharmacology

### Pharmacokinetics

Table 11. Age-Associated Pharmacokinetics

Parameter	Age Effect	Implications
<b>Absorption</b> (less significant)	Increased gastric pH Decreased splanchnic blood flow, GI absorptive surface and dermal vascularity; delayed gastric emptying	Drug-drug and drug-food interactions are more likely to affect absorption
<b>Distribution</b>	Increased total body fat and $\alpha$ 1-glycoprotein Decreased lean body mass, total body water and albumin	Lipophilic drugs have a larger volume of distribution Decreased binding of acidic drugs, increased binding of basic drugs
<b>Metabolism</b> (less significant)	Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)	Lower doses may be therapeutic
<b>Elimination</b>	Decreased renal blood flow, GFR, tubular secretion and renal mass	For every x% reduction in clearance, decrease the dose by x% and increase the interval by x%

#### WHO's Pain Relief Ladder



#### Death Rattle

Noise caused by the oscillatory movement of mucous secretions in the upper airway with inspiration and expiration.



#### Nociceptive Pain

Somatic: localized to bone/skin/joint/muscle; gnawing, dull pain  
Visceral: not well localized; crampy pain, pressure

#### Neuropathic Pain

Burning, shooting, radiating pain; localized to dermatomal regions



#### Opioid Equivalent Doses (to 10 mg of IV morphine)

Opioid	SC/IV dose	PO dose
Morphine	10 mg	20-30 mg
Codeine	Not recommended	180-240 mg
Oxycodone	Not recommended	10-15 mg
Hydromorphone	2 mg	4-6 mg

Fentanyl transdermal 25 µg/h = morphine 90 mg PO/24 h, however fentanyl takes 12-16 h to reach steady state



Serum creatinine does not reflect creatinine clearance in the elderly.

Instead, use:  
 $CrCl = \frac{(\text{weight in kg})(140 - \text{age})(1.23)}{72}$  (mL/min) (serum creatinine in µmol/L)

Multiply by 0.85 for females.

## Pharmacodynamics

### Drug Sensitivity

- changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives, antipsychotics, digoxin and narcotics
- decreased sensitivity to  $\beta$ -blockers in majority of elderly patients, though some may have increased sensitivity

### Decreased Homeostasis

- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

## Polypharmacy

### Definition

- prescription, administration or use of many medications at the same time

### Epidemiology

- in Canada, over 25% of elderly women and about 20% of elderly men reported using  $\geq 3$  medications
- hospitalized elderly are given an average of 10 medications during admission

### Risk Factors for Non-Compliance

- risk of non-compliance correlates with medication factors, not age
  - number of medications – compliance with 1 medication is 80%, but drops to 25% with  $\geq 6$  medications
- increased dosing frequency, complicated container design, financial constraints, and cognitive impairment

### Adverse Drug Reactions (ADRs)

- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in the elderly
  - intrinsic: co-morbidities, age-related changes in pharmacokinetics and pharmacodynamics
  - extrinsic: number of medications, multiple prescribers, unreliable drug history
- 90% of ADRs are from: ASA, analgesics, anticoagulants, antimicrobials, antineoplastics, digoxin, diuretics, hypoglycemics, steroids

### Preventing Polypharmacy

- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical co-morbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an ADR with another medication

## Inappropriate Prescribing in the Elderly

### Epidemiology

- the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

### Beers Criteria

- a list of medications to avoid in adults 65 and older due to safety concerns
- examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives
- the elderly are also often under-treated (ACEI, ASA,  $\beta$ -blockers, thrombolytics, warfarin)



### Benzodiazepines of Choice in the Elderly

#### LOT

Lorazepam  
Oxazepam  
Temazepam



### Approach to Medication Review in the Elderly

#### NO TEARS

Need and indication  
Open-ended questions (to get patient's perspective on medications)  
Tests and monitoring (to assess disease control)  
Evidence and guidelines  
Adverse events  
Risk reduction (of adverse events such as falls)  
Simplification/switches



New medications: Start Low, Go Slow!



### Principles for Prescribing in the Elderly

#### CARED

Caution/Compliance  
Age (adjust dosage for age)  
Review regimen regularly  
Educate  
Discontinue unnecessary medications

*Geriatric Pearls.* Philadelphia: FA Davis Company, 1999.



Adverse drug reactions in the elderly may present as delirium, falls, fractures, urinary incontinence/retention or fecal incontinence/impaction.



### Beers Criteria

For full list of medications, consult the following reference:  
The American Geriatrics Society 2012 Beers Criteria Update Expert Panel  
*J Am Geriatr Soc* 2012;60(4):616-31  
<http://www.americangeriatrics.org>



## Common Medications

Table 12. Common Medications

Drug Name	Brand Name	Dosing Schedule	Indications	Contraindications	Side Effects	Mechanism of Action
<b>ANALGESICS (non-opioid)</b>						
<b>acetaminophen</b>	Tylenol®	325-650 mg PO q4-6h prn (up to 4 g/d)	Fever, mild pain	Lower doses for hepatic and renal disease, chronic alcoholism, known hypersensitivity	Hepatotoxicity (in overdose)	Prostaglandin-synthesis inhibition, no anti-inflammatory effects
<b>ibuprofen</b>	Advil® Motrin®	200-800 mg PO q4-6h prn (up to 1200 mg/d)	Mild to moderate pain, inflammatory disorders, fever	Active GI bleed/ulcer disease, known hypersensitivity, severe renal or hepatic disease Geriatrics: more susceptible to adverse effects	Dyspepsia, nausea, diarrhea, dizziness, rash, GI toxicity (ulcer, perforation, bleed)	Prostaglandin-synthesis inhibition, anti-inflammatory effects
<b>celecoxib</b>	Celebrex®	200 mg PO daily or 100 mg PO bid	Osteoarthritis, rheumatoid arthritis, FAP	Cardiovascular or cerebrovascular disease, CABG (peri-op), sulfonamide or ASA/NSAID allergy, active GI bleed/ulcer, IBD, severe renal or hepatic disease, hyperkalemia	GI symptoms (pain, diarrhea, dyspepsia, flatulence), GI bleed, serious cardiovascular events	COX-2 inhibitor, analgesic, anti-inflammatory and anti-pyretic effects
<b>ANALGESICS (opioid) – see <a href="#">Anesthesia and Peri-Operative Medicine</a>, A26</b>						
<b>ANTI-HYPERTENSIVES</b>						
<b>thiazide diuretic</b> e.g. hydrochlorothiazide	Hydrazide®	12.5-25 mg PO daily	Hypertension, edema	Anuria, hepatic coma, pre-coma, known sensitivity to thiazides	Hypotension, transient hyperlipidemia, hypokalemia and other electrolyte disturbances, hyperuricemia, GI symptoms	Inhibition of Na <sup>+</sup> /Cl <sup>-</sup> co-transporter
<b>ACEI</b> e.g. ramipril	Altace®	2.5-20 mg PO daily	Essential hypertension, post-MI, cardiovascular disease, renal protection	Known hypersensitivity, angioedema	Hypotension, cough, headache, dizziness, asthenia, chest pain, nausea, peripheral edema, arthritis, dyspnea, angioedema, hyperkalemia	Inhibition of angiotensin-converting enzyme
<b>ARB</b> e.g. losartan	Cozaar®	50-100 mg PO daily	Essential hypertension (± diabetes mellitus)	Known hypersensitivity	Dizziness, hypotension, fatigue, headache, hyperkalemia	Antagonizes angiotensin II via blockade of the angiotensin type 1 receptor
<b>DHP CCB</b> e.g. amlodipine	Norvasc®	2.5-10 mg PO daily (initially)	Essential hypertension, chronic stable angina	Known hypersensitivity, severe hypotension, caution in aortic stenosis	Edema, muscle cramps, dizziness, headache, constipation, heartburn	Calcium ion influx inhibition
<b>COGNITIVE ENHANCERS</b>						
<b>donepezil</b>	Aricept®	5-10 mg PO daily	Moderate to severe dementia of Alzheimer's type	Known hypersensitivity, caution in pulmonary disease, sick sinus syndrome, seizure disorder	N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion	Reversible inhibition of acetylcholinesterase
<b>galantamine</b>	Reminyl®	8-12 mg PO bid	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, caution in sick sinus syndrome, seizure disorder, pulmonary disease, low body weight	N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion	Reversible inhibition of acetylcholinesterase
<b>rivastigmine</b>	Exelon®	1.5 mg PO daily (starting) up to 6 mg PO bid	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, severe hepatic disease, caution in sick sinus syndrome, pulmonary disease, seizure disorder	N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion	Acetylcholinesterase inhibition (reversible but very slow)
<b>memantine</b>	Ebixa®/ Namenda® (Can)/(U.S.)	5 mg PO daily (starting) up to 10 mg PO bid	Mild to moderate dementia of Alzheimer's type	Known hypersensitivity, conditions that alkalize urine, caution in cardiovascular conditions	Agitation, fatigue, dizziness, headache, hypertension, constipation	NMDA-receptor antagonist

**Table 12. Common Medications** (continued)

Drug Name	Brand Name	Dosing Schedule	Indications	Contraindications	Side Effects	Mechanism of Action
<b>LAXATIVES</b>						
<b>bran</b>	All-Bran®	1 cup/d	Constipation		Bloating, flatus	Bulk-forming laxative
<b>psyllium</b>	Metamucil® Prodiem Plain®	1 tsp PO tid	Constipation, hypercholesterolemia	N/V, abdominal pain, obstruction	Bloating, flatus	Bulk-forming laxative
<b>lactulose</b>	Chronulac® Cephulac® Kristalose®	15-30 cc PO daily/bid	Constipation, hepatic encephalopathy, bowel evacuation following barium exam	Patients on low galactose diets Abdominal pain, N/V	Flatus, cramps, nausea, diarrhea	Hyperosmolar agent, lowers pH of colon to decrease blood ammonia levels
<b>senna</b>	Senokot®/ Ex-lax® Glyssennid®	1-2 tabs PO daily or 10-15 cc syrup PO daily	Constipation	Abdominal pain, N/V	Cramps, griping, dependence	Stimulant laxative
<b>bisacodyl</b>	Dulcolax®	5-15 mg PO (10 mg PR)	Constipation	Ileus, obstruction, abdominal pain, N/V, severe dehydration	Cramps, pain, diarrhea	Stimulant laxative
<b>PARKINSONIAN AGENTS</b> – see <a href="#">Neurology, N48</a>						
<b>SLEEPING MEDICATIONS</b>						
<b>zopiclone</b>	Imovane®	3.75 mg PO qhs (initially)	Insomnia	Known hypersensitivity, caution in myasthenia gravis, severe hepatic disease Geriatrics: dose reduction (dose-related adverse events)	Bitter taste, palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor, sweating	Short-acting hypnotic (no tolerance effects)
<b>temazepam</b>	Restoril®	15 mg PO qhs	Short-term management of insomnia	Known hypersensitivity, myasthenia gravis, sleep apnea Geriatrics: dose reduction recommended	Drowsiness, dizziness, impaired coordination, hangover, lethargy, dependence	Benzodiazepine: generalized CNS depression mediated by GABA
<b>lorazepam</b>	Ativan®	0.5 mg PO qhs (initially)	Anxiety, insomnia	Known hypersensitivity, myasthenia gravis, narrow- angle glaucoma Geriatrics: dose reduction recommended	Dizziness, drowsiness, lethargy, dependence	Benzodiazepine: generalized CNS depression mediated by GABA

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in the elderly

## Landmark Geriatric Trials

Trial	Reference	Results
Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease	NEJM 2012; 366:893-903	Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer's disease
Early palliative care for metastatic lung cancer	NEJM 2010; 363:733-742	Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end-of-life but longer survival
Hip protectors for fracture prevention	NEJM 2000; 343:1506-1513	The risk of hip fracture can be reduced in frail elderly adults by the use of an anatomically designed external hip protector
HYVET	NEJM 2008; 358:1887-1898	Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in adults 80 yr or older is beneficial
PROFET	Lancet 1999; 353:93-97	Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment
Yale Delirium Prevention Trial	NEJM 1999; 340:669-676	A risk-factor intervention strategy can result in significant reductions in the number and duration of episodes of delirium in hospitalized older patients

# References

## Health Status

Heron M. Deaths: leading causes for 2004. Health E-Stats; 2007.  
Minino AM. Death in the United States. NCHS Data Brief 2009;No64:2011.  
Statistics Canada. Deaths, by selected grouped causes and sex, Canada, provinces and territories, annual. Ottawa, 2005.

## Physiology and Pathology of Aging

Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL. Harrison's principles of internal medicine. New York: McGraw-Hill, 2004.

## Constipation

Higgins PDR, Johanson JF. Epidemiology of constipation in North America: a systematic review. Am J Gastroenterol 2004;99:750-759.  
Reuben DB, Herr KA, Pacala JT, et al. Geriatrics at your fingertips, 13th ed. New York: The American Geriatrics Society, 2011.  
Rao SSC, Go JT. Update on the management of constipation in the elderly: new treatment options. Clin Interv Aging 2010;5:163-171.

## Delirium, Dementia and Depression

British Geriatrics Society and Royal College of Physicians. Guidelines for prevention, diagnosis and management of delirium in older people. Concise guidance to good practice series. 2006;No.6.  
Young J, Murthy L, Westby M, et al. Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ 2010;341:c3704.

## Elder Abuse

Health Canada. The Canadian guide to clinical preventative health care. Ottawa: Canadian Task Force on Preventative Health Care, 2002.  
Kergoat MJ. Preventative health care in the elderly. Can J CME 2000.  
Lachs M, Pillemer K. Elder abuse. Lancet 2004;364:1192-1263.  
NICE. Case: caregiver abuse screen. 2010. Available from: <http://www.nicenet.ca/files/Case.pdf>.

## Falls

Fuller G. Falls in the elderly. Am Fam Phys 2001;61:2159-2172.  
Ganz DA, Bao Y, Shekelle PE, Rubenstein LZ. Will my patient fall? JAMA 2007;297:77-86.  
Gillespie LD, Gillespie WJ, Robertson MC, et al. Interventions for preventing falls in elderly people. Cochrane DB Syst Rev 2003;Issue 4.  
Goldist B, Turpic I, Borins M. Essential geriatrics: managing 6 conditions. Patient Care 1997;8:61-74.  
Kiel DP, Rose BD, Wellesly MA (editors). Overview of falls in the elderly. UpToDate. 2005.  
Reuben DB, Herr KA, Pacala JT, et al. Geriatrics at your fingertips, 13th ed. New York: The American Geriatrics Society, 2011.  
Tinetti ME, Baker DI, McAvay G, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. NEJM 1994;331:821-827.

## Frailty

Robertson RG, Montagnini M. Geriatric failure to thrive. Am Fam Phys 2004;70:343-348.  
Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.  
Sarkisian CA, Laches MS. "Failure to thrive" in older adults. Ann Intern Med 1996;124:1072-1078.  
Verdery RB. Clinical evaluation of failure to thrive in older people. Clin Geriatr Med 1997;13:769-778.

## Hazards of Hospitalization

Creditor MC. Hazards of Hospitalization of the Elderly. Ann Intern Med 1993;118:219-223.  
Inouye S, Bogardus ST, Charpentier PA, et al. A multi-component intervention to prevent delirium in hospitalized older patients. NEJM 1999;340:669-676.  
Sager MA, Franke T, Inouye SK, et al. Functional outcomes of acute medical illness and hospitalization in older persons. Arch Internal Med 1996;156:645-652.  
Wilson RS, Herbert LE, Scherr PA, et al. Cognitive decline after hospitalization in a community population of older persons. Neurology 2012;78:950-956.

## Hypertension

Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. NEJM 2008;358:1887-1898.  
Reuben DB, Herr KA, Pacala JT, et al. Geriatrics at your Fingertips. 13th ed, New York: The American Geriatrics Society, 2011.  
Whelton PK, Appel LJ, Espeland MA, et al. The 2001 Canadian hypertension recommendations. Perspect in Cardiol 2002;38-46.

## Immunizations

Rivetti D, et al. Vaccines for preventing influenza in the elderly. Cochrane DB Syst Rev 2006;19:3:CD004876.

## Malnutrition

Halsted CH. Harrison's principles of internal medicine, 16th ed. Kasper, DL. 2004. Chapter: Malnutrition and nutritional assessment. p411-415.

## Pressure Ulcers

Berlowitz D, Rose BD (editor). Pressure ulcers: staging; epidemiology; pathogenesis; clinical manifestations. UpToDate. Wellesly, MA. 2005.

## Driving Competency

AMA. Physicians guide to assessing and counseling older drivers. National Highway Traffic Safety Administration, 2006.  
CMA. Determining medical fitness to drive: a guide for physicians. Ottawa, 2006.  
Grabowski DC, Campbell CM, Morrissey MA. Elderly licensure laws and motor vehicle fatalities. JAMA 2004;291:2840-2846.  
Hogan DB. Systematic review of driving risk and the efficacy of compensatory strategies in persons with dementia. J Am Geriatr Soc 2007;55:878-884.  
Wiseman EJ. The older driver: a handy tool to assess competence behind the wheel. Geriatrics 1996;51:36-45

## Health Care Institutions

Government of Ontario. Reports on long-term care homes. Queen's Printer for Ontario, 2007.

## Palliative and End-of-Life Care

AGS Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc 2002;50:Supplement.  
Bruera, E, Kuehn N, Miller MJ, Selmer P, et al. The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative care patients. J Pall Care 1991;7:6-9.  
Knowles S. Symptom management in palliative care. On Continuing Practice 1993;20:20-5.  
Medical care of the dying, 4th ed. Victoria: Victoria Hospice Society, 2006. Chapter: Palliative performance scale, version 2. p120-121.  
The World Health Association. Cancer – The WHO's pain ladder. 2001. Available from: <http://www.who.int/cancer/palliative/painladder/en/>.

## Geriatric Pharmacology

American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults. JAGS 2012. Available from: <http://www.americangeriatrics.org>.  
Carlson JE. Perils of polypharmacy: 10 steps to prudent prescribing. Geriatrics 1996;51:26-35.  
Fick DM, Cooper JW, Wade WE, et al. Updating the Beers Criteria for potentially inappropriate medication use in older adults. Arch Intern Med 2003;163:2716-2724.  
Fordyce, M. Geriatric pearls. Philadelphia: FA Davis, 1999.  
Lewis, T. Using the NO TEARS tool for medication review. BMJ 2004;329:434.

Emily Brander, Jena Hall, Katherine McLean and Marina Vainder, chapter editors

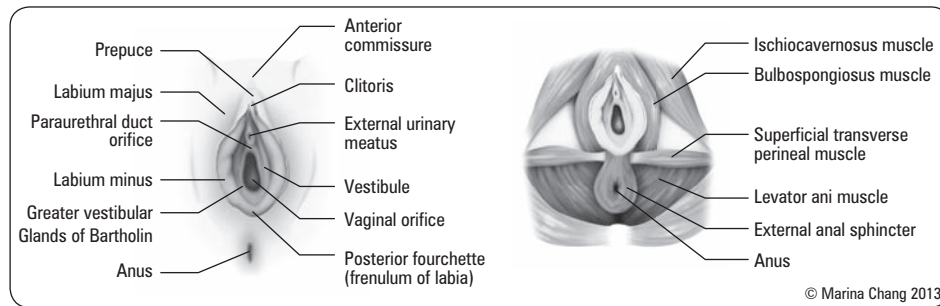
Jieun Kim and Daniel Soong, associate editors

Jeff Martin, EBM editor

Dr. Sarah Ferguson, Dr. Sari L. Kives and Dr. Fay Weisberg, staff editors

<b>Acronyms</b> .....	<b>2</b>	<b>Gynecological Infections</b> .....	<b>24</b>
<b>Basic Anatomy Review</b> .....	<b>2</b>	Physiologic Discharge	
<b>Menstruation</b> .....	<b>3</b>	Vulvovaginitis	
Stages of Puberty		Sexually Transmitted Infections (STIs)	
Menstrual Cycle		Bartholinitis/Bartholin Gland Abscess	
Premenstrual Syndrome (PMS)		Pelvic Inflammatory Disease (PID)	
Premenstrual Dysphoric Disorder (PMDD)		Toxic Shock Syndrome	
<b>Differential Diagnoses of Common Presentations</b> .....	<b>6</b>	Surgical Infections	
Abnormal Uterine Bleeding (AUB)		<b>Sexual Abuse</b> .....	<b>31</b>
Dysmenorrhea		<b>Sexuality and Sexual Dysfunction</b> .....	<b>31</b>
Vaginal Discharge/Pruritus		<b>Menopause</b> .....	<b>32</b>
Pelvic Pain		Hormone Replacement Therapy (HRT)	
Pelvic Mass		<b>Urogynecology</b> .....	<b>34</b>
Dyspareunia		Pelvic Relaxation/Prolapse	
<b>Common Investigations</b> .....	<b>8</b>	Urinary Incontinence	
Bloodwork		<b>Gynecological Oncology</b> .....	<b>36</b>
Imaging		Uterus	
<b>Common Procedures</b> .....	<b>9</b>	Ovary	
Genital Tract Biopsy		Cervix	
Colposcopy		Vulva	
Vacuum Aspiration		Vagina	
Dilatation and Curettage (D&C)		Fallopian Tube	
Laparoscopy		Gestational Trophoblastic Disease/Neoplasia (GTD/GTN)	
Hysteroscopy		<b>Common Medications</b> .....	<b>51</b>
Endometrial Ablation		<b>References</b> .....	<b>52</b>
Hysterectomy			
<b>Disorders of Menstruation</b> .....	<b>12</b>		
Amenorrhea			
Abnormal Uterine Bleeding (AUB)			
Dysmenorrhea			
<b>Endometriosis</b> .....	<b>16</b>		
<b>Adenomyosis</b> .....	<b>17</b>		
<b>Leiomyomata (Fibroids)</b> .....	<b>17</b>		
<b>Contraception</b> .....	<b>19</b>		
Hormonal Methods			
Intrauterine Device (IUD)			
Emergency Postcoital Contraception (EPC)			
<b>Infertility</b> .....	<b>22</b>		
Female Factors			
Male Factors			

## Basic Anatomy Review



**Figure 1. Vulva and perineum**

### A. EXTERNAL GENITALIA (Figure 1)

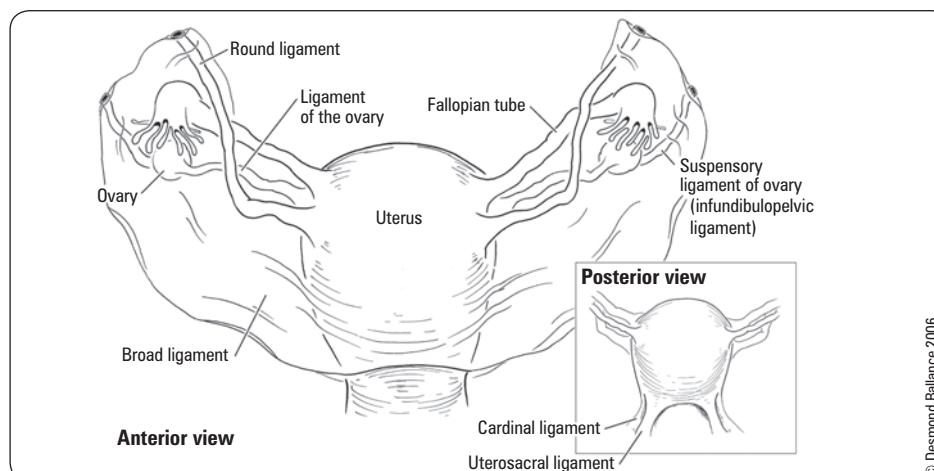
- referred to collectively as the vulva
- blood supply: internal pudendal artery
- sensory innervation: pudendal nerve
- lymphatic drainage: inguinal nodes

### B. VAGINA

- muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
- lined by rugated, stratified-squamous epithelium
- upper vagina separated by cervix into anterior, posterior and lateral fornices
- blood supply: vaginal branch of internal pudendal artery with anastomoses from uterine, inferior vesical and middle rectal arteries

### C. UTERUS

- thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - uterine corpus
    - ♦ blood supply: uterine artery (branch of the internal iliac artery)
  - cervix
    - ♦ blood supply: cervical branch of uterine artery
- supported by the pelvic diaphragm, the pelvic organs and 4 paired sets of ligaments
  - round ligaments: travel from anterior surface of uterus, through broad ligaments and inguinal canals then terminate in the labia majora
    - ♦ function: anteversion
    - ♦ blood supply: Sampson's artery (branch of uterine artery running through round ligament)
  - uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
    - ♦ function: mechanical support for uterus and contain autonomic nerve fibres
  - cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
    - ♦ function: mechanical support, prevent prolapse
  - broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels and lymphatics
- infundibulopelvic ligament: continuous tissue that connects ovary to pelvic wall
  - contains the ovarian artery, ovarian vein, ovarian plexus, lymphatic vessels
- position of the uterus (Figure 3)
  - anteverted (majority)
  - retroverted



**Figure 2. External genital organs**

## Acronyms

$\beta$ -hCG	beta-human chorionic gonadotropin
AFP	alpha-fetoprotein
AIS	androgen insensitivity syndrome
AUB	abnormal uterine bleeding
BMI	body mass index
BSO	bilateral salpingo-oophorectomy
CAH	congenital adrenal hyperplasia
CMV	cytomegalovirus
D&C	dilatation and curettage
DES	diethylstilbestrol
DHEA	dihydroepiandrosterone
DM	diabetes mellitus
DUB	dysfunctional uterine bleeding
EPC	emergency postcoital contraception
FSH	follicle stimulating hormone
GA	gestational age
GIFT	gamete intrafallopian transfer
GnRH	gonadotropin-releasing hormone
GTD	gestational trophoblastic disease
GTN	gestational trophoblastic neoplasia
HMG	human menopausal gonadotropin
HPO	hypothalamic-pituitary-ovarian
HRT	hormone replacement therapy
HSG	hysterosalpingography
HSIL	high grade squamous intraepithelial lesion
HSV	herpes simplex virus
IBD	inflammatory bowel disease
ICSI	intracytoplasmic sperm injection
ITP	immune thrombocytopenic purpura
IUD	intrauterine device
IUI	intrauterine insemination
IVDU	intravenous drug use
IVF	in vitro fertilization
IVM	in vitro maturation
JRA	juvenile rheumatoid arthritis
LEEP	loop electrosurgical excision procedure
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
LMP	last menstrual period
LN	lymph node
LNMP	last normal menstrual period
MRKH	Mayer-Rokitansky-Küster-Hauser
NK	natural killer
OCP	oral contraceptive pill
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
PG	prostaglandin
PID	pelvic inflammatory disease
PMDD	premenstrual dysphoric disorder
PMN	polymorphonuclear neutrophils
PMS	premenstrual syndrome
RPR	rapid plasma reagin
SERMs	selective estrogen receptor modifiers
SHBG	sex hormone binding globulin
SHG	sonohysterography
STI	sexually transmitted infection
TAH	total abdominal hysterectomy
TB	tuberculosis
TET	tubal embryo transfer
TH	total hysterectomy
TSH	thyroid stimulating hormone
TZ	transformation zone
VDRL	venereal disease research laboratory
vWD	von Willebrand's disease
w/d	withdrawal
ZIFT	zygote intrafallopian transfer

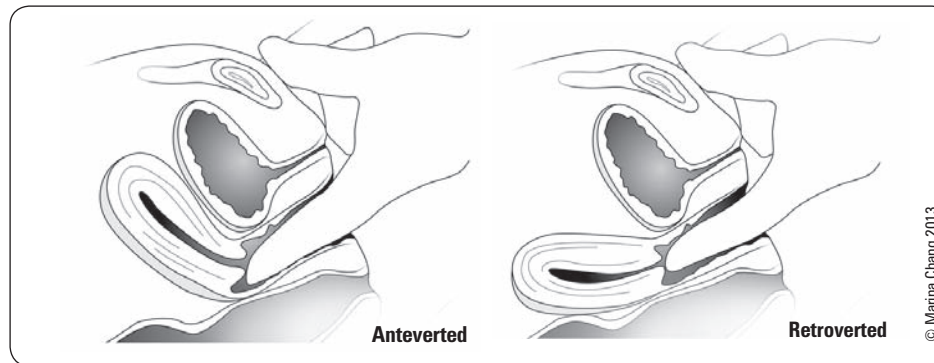


Figure 3. Positioning of uterus

#### D. FALLOPIAN TUBES

- 8-14 cm muscular tubes extending laterally from the uterus to ovary
- interstitial, isthmic, ampullary and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

#### E. OVARIES

- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

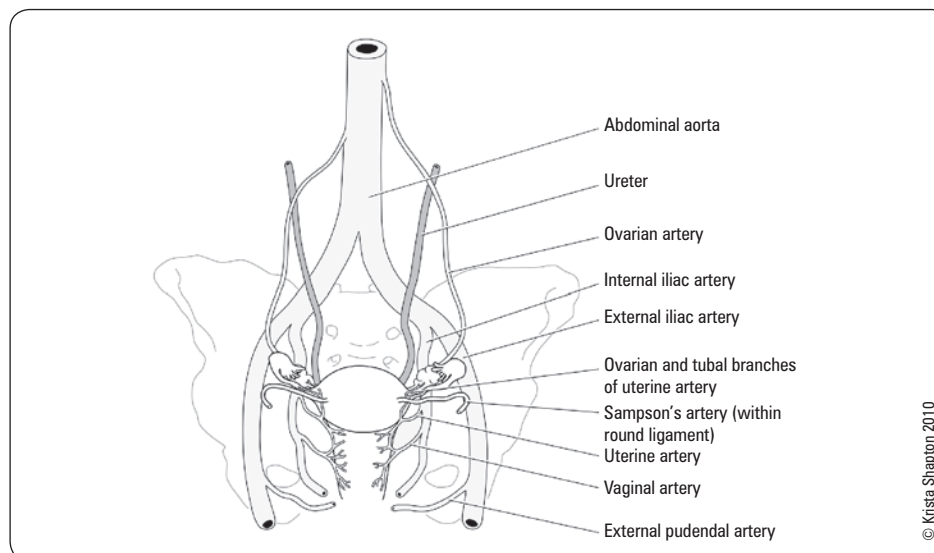


Figure 4. Vascular supply

**Anteversion:** forward-tilted uterus.

**Anteflexion:** bending of uterus so the fundus is thrust forward.

**Retroversion:** backward-tilted uterus.

**Retroflexion:** bending of uterus so the fundus is thrust backward.



Determination of uterine position by clinical exam:

- If cervix faces anteriorly, i.e. toward vaginal orifice, more likely **RETROVERTED UTERUS**
- If cervix faces posteriorly, i.e. toward sacrum or rectum, more likely **ANTVERTED UTERUS**
- If uterus palpable on bimanual exam, more likely **ANTEVERTED UTERUS**



**"Water under the bridge"**

The ureters run posterior to the uterine arteries.



**Stages of Puberty**

**"Boobs, Pubes, Grow, Flow"**

Thelarche, Pubarche, Growth spurt, Menarche.



**Tanner Stage**

Thelarche

- None
- Breast bud
- Further enlargement of areola and breasts with no separation of contours
- 2° mound of areola and papilla
- Areola recessed to general contour of breast – adult

Pubarche

- None
- Downy hair along labia only
- Darker/coarse hair extends over pubis
- Adult type covers smaller area, no thigh involvement
- Adult hair in quantity and type. Extends over thighs

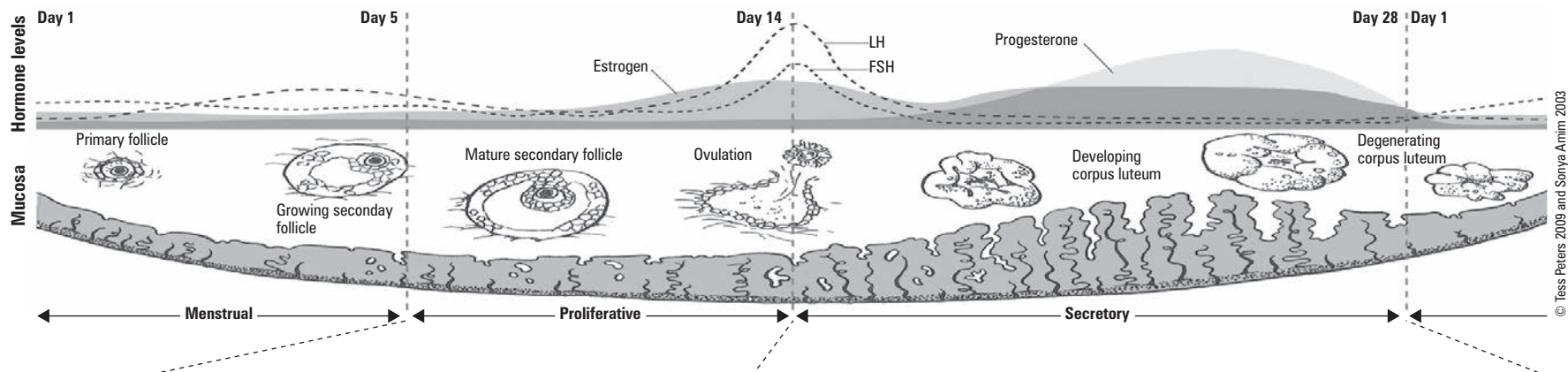
## Menstruation

### Stages of Puberty

- see [Pediatrics](#), P31
- adrenarche: increase in secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding



# Menstrual Cycle



© Tess Peters 2009 and Sonya Anim 2003

	FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)			LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)		
	Early	Mid	Late	OVULATION	Early-Mid	Late
Initiating events	↓ E and ↓ P (from end of previous cycle)	↑ FSH acts on ovarian granulosa cells	Growing follicles continue to secrete E	Sudden switch from negative to positive feedback (E and P now ↑ FSH & LH)	Switch back to negative feedback	No fertilized oocyte
HPO axis	↑ GnRH pulse frequency ↑ FSH ↑ LH pulse frequency	↑ E from follicles (ovary)		↑↑ LH pulse amplitude (LH surge)	↓ LH	
Hormones			↑ E from follicles, esp. from dominant follicle	E peaks → LH surge → ovulation	↑ P from corpus luteum	↓ P secondary to degeneration of corpus luteum
Feedback on HPO axis		Negative feedback E → ↓ FSH, ↓ LH		Positive feedback: E and P → ↑ FSH, ↑ LH	Negative feedback P → ↓ FSH, ↓ LH	
Ovaries	↑ FSH → follicular growth in 3-30 follicles	↑ follicular growth (by reducing atresia) → ↑ E	Dominant follicle persists, remainder undergo atresia Granulosa cells luteinize → produce P	~36 h after LH surge, dominant follicle releases oocyte; corpus luteum (remnant of dominant follicle) produces P		Cessation of P from corpus luteum
Endometrium	Menses from P withdrawal (from end of previous cycle)		E builds up endometrium		P stabilizes endometrium	Withdrawal of P → menses
Cervical Mucus		Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy				Opaque, scant amount, Spinnbarkeit 1-2 cm

E = estrogen; P = progesterone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone; HPO = hypothalamic-pituitary-ovarian

Figure 5. Events of the normal menstrual cycle

## Characteristics

- Menarche 10-15 yr
- Average 12.2 yr
- Entire cycle  $28 \pm 7$  d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

## Estrogen

ESTROGEN is the main hormone in the follicular/proliferative phase and is stimulated by FSH. Increased estrogen mainly decreases FSH. The majority of estrogen is secreted by the dominant follicle.

Estrogen effects:

- On the follicles in the ovaries:
  - Reduces atresia
- On the endometrium:
  - Proliferation of glandular and stromal tissue
- On all target tissues:
  - Decreases E receptors

## Progesterone

PROGESTERONE is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone mainly decreases LH and is secreted by the corpus luteum (remnant of dominant follicle).

Progesterone effects:

- On the endometrium:
  - Cessation of mitoses (stops building endometrium up)
  - "Organization" of glands (initiates secretions from glands)
  - Inhibits macrophages, interleukin-8 and enzymes from degrading endometrium
- On all target tissues:
  - Decrease E receptors (the "anti-estrogen" effect)
  - Decrease P receptors

## Premenstrual Syndrome (PMS)

- synonyms: “ovarian cycle syndrome,” “menstrual molimina” (moodiness)

### Etiology

- not completely understood, multifactorial, genetics likely play a role
- CNS-mediated neurotransmitter interactions with sex steroids (progesterone, estrogen and testosterone)
- serotonergic dysregulation – currently most plausible theory

### Diagnostic Criteria for Premenstrual Syndrome

- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness, abdominal bloating, headache, swelling of extremities
- symptoms relieved within 4 d of onset of menses
- symptoms present in the absence of any pharmacologic therapy, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or economic performance

### Treatment

- goal: symptom relief
- psychological support
- diet/supplements
  - avoid sodium, simple sugars, caffeine and alcohol
  - calcium (1200-1600 mg/d), magnesium (400-800 mg/d), vitamin E (400 IU/d), vitamin B<sub>6</sub>
- medications
  - NSAIDs for discomfort, pain
  - spironolactone for fluid retention: used during luteal phase
  - SSRI antidepressants: used during luteal phase x 14 d or continuously
  - OCP: primarily beneficial for physical/somatic symptoms
  - danazol: an androgen that inhibits the pituitary-ovarian axis
  - GnRH agonists if PMS is severe and unresponsive to treatment
- mind/body approaches
  - regular aerobic exercise
  - cognitive behavioural therapy
  - relaxation, light therapy biofeedback and guided imagery
- herbal remedies (variable evidence)
  - evening primrose oil, black cohosh, St. John's wort, kava, ginkgo, agnus castus fruit extract
- BSO if symptoms severe



### Premenstrual Syndrome

Physiological and emotional disturbances that occur 1-2 wk prior to menses and last until a few days after onset of menses. Common symptoms include depression, irritability, tearfulness and mood swings.

## Premenstrual Dysphoric Disorder (PMDD)

### Definition

- official diagnosis in the DSM-IV-TR
- described as a more severe form of PMS with specific diagnostic criteria
- treatment with SSRIs (first line), and Yaz® OCP (highly effective)

# Differential Diagnoses of Common Presentations

## Abnormal Uterine Bleeding (AUB)



- see *Disorders of Menstruation*, GY14
- definition: change in frequency, duration or amount of menstrual flow
- classified as amenorrhea, oligomenorrhea, menorrhagia/hypermenorrhea, hypomenorrhea, metrorrhagia, menometrorrhagia, polymenorrhea, postmenopausal bleeding
  - hypomenorrhea: bleeding that is decreased in amount
  - oligomenorrhea: bleeding occurring at intervals >35 d
  - polymenorrhea: bleeding occurring at intervals <21 d
  - menorrhagia/hypermenorrhea: bleeding at regular intervals that is prolonged in duration (>7 d) or excessive in amount (>80 cc per menstrual cycle)
  - metrorrhagia: bleeding at irregular intervals, particularly between expected menstrual periods
  - menometrorrhagia: excessive bleeding at usual time of menstrual periods and at other irregular intervals
  - postmenopausal bleeding: any bleeding that presents >1 yr after menopause; must rule out endometrial cancer



Postmenopausal bleeding is endometrial cancer until proven otherwise.

## Dysmenorrhea



- see *Disorders of Menstruation*, GY15
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease (PID)
  - IUD (copper)
  - foreign body

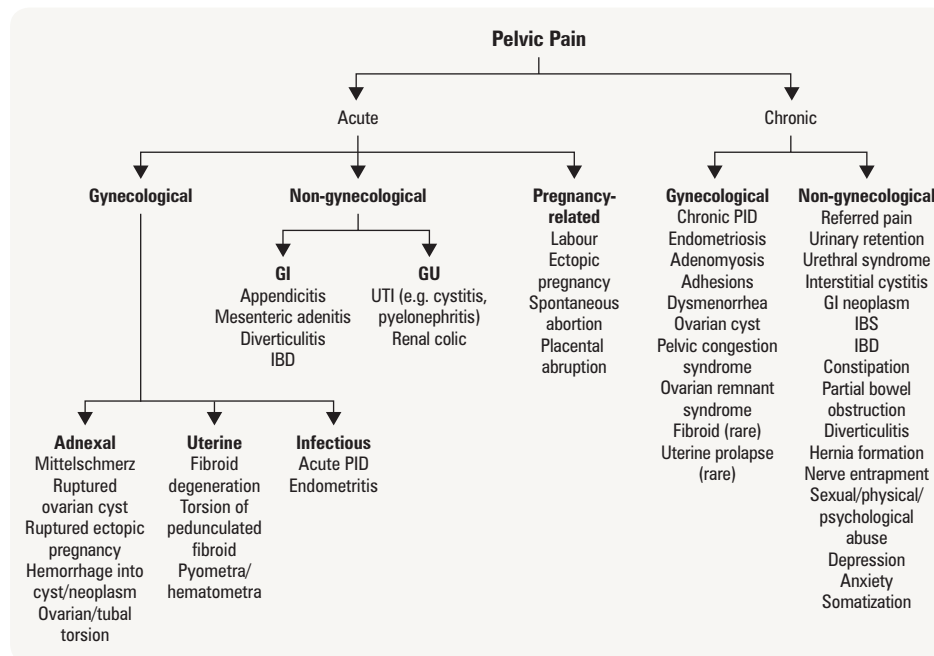
### Dysmenorrhea

Painful menstruation.

## Vaginal Discharge/Pruritus

- see *Gynecological Infections*, GY24
- physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
    - vulvovaginitis: candidiasis, trichomoniasis, bacterial vaginosis (BV), polymicrobial superficial infection
    - chlamydia, gonorrhea
    - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)

## Pelvic Pain



20% of chronic pelvic pain patients have a history of previous sexual abuse/assault. Remember to ask about it!

### Pyometra

Pus within the uterine cavity.

### Hematometra

Blood within the uterine cavity.

### Hydrometra

Fluid within the uterine cavity.

Figure 6. Approach to pelvic pain

## Pelvic Mass

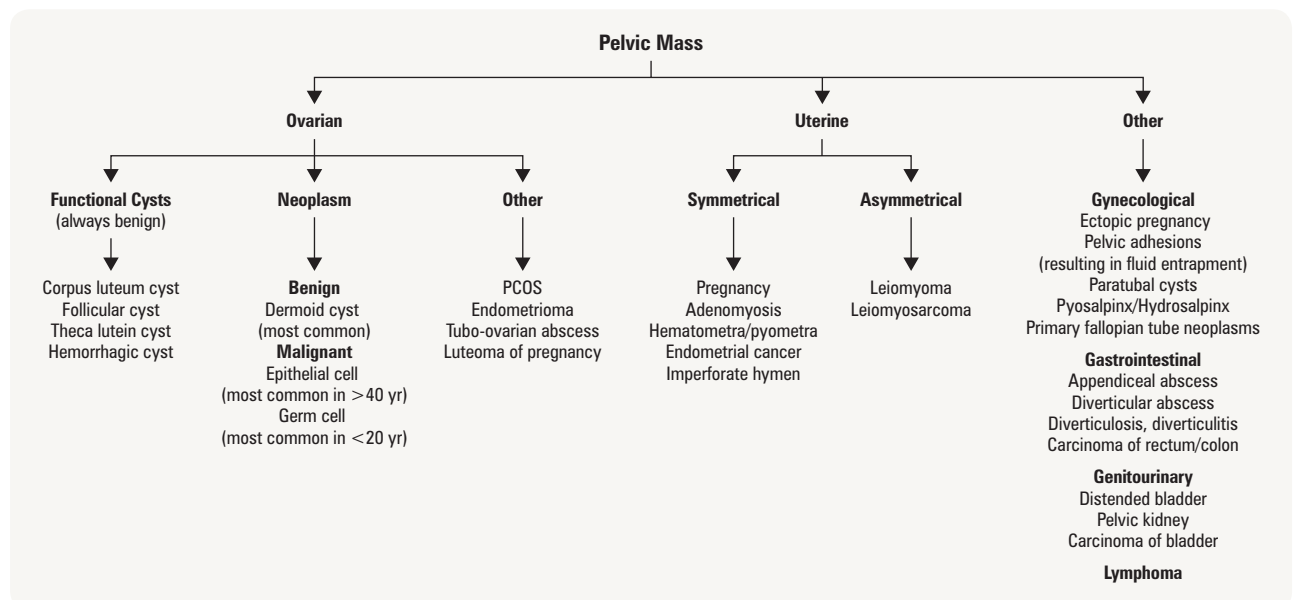
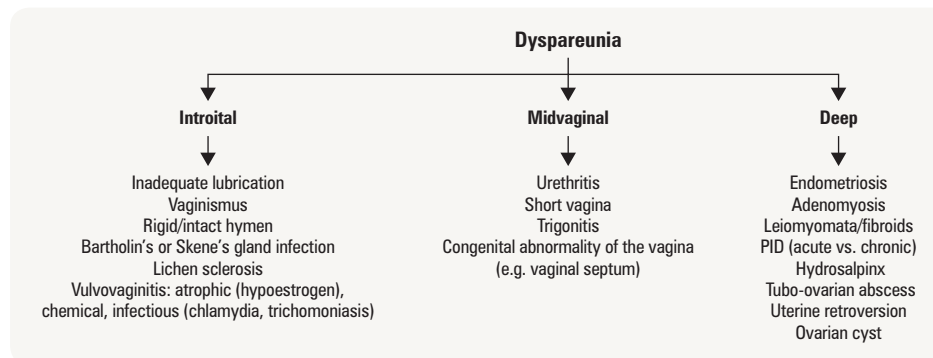


Figure 7. Differential diagnosis of pelvic mass

## Dyspareunia



**Dyspareunia**  
Painful intercourse.

Figure 8. Approach to dyspareunia

## Common Investigations

### Bloodwork

- CBC
  - evaluation of severity of abnormal uterine bleeding, pre-op investigation ± ferritin if anemic
- $\beta$ -hCG
  - investigation of possible pregnancy, ectopic pregnancy, ovarian germ cell tumour
  - work-up for GTD/GTN
  - monitored after medical management of ectopic pregnancy and GTN to assess for cure or recurrence
- LH, FSH, TSH, free  $T_4$ , prolactin, DHEA, testosterone, estradiol, androstenedione
  - investigation of amenorrhea, menstrual irregularities, menopause, infertility



Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have  $\beta$ -hCG measured.

### Imaging



#### Ultrasound (U/S)

- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if  $\beta$ -hCG  $\geq 1500$  ( $\beta$ -hCG must be  $\geq 6500$  for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterize fibroids
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal women

#### Sonohysterography (SHG)

- saline infusion into endometrial cavity expands endometrial cavity, improving visualization of uterus and fallopian tubes
- useful for investigation of:
  - abnormal uterine bleeding (AUB)
  - uncertain endometrial findings on transvaginal U/S
  - infertility (tubal patency)
  - congenital/acquired uterine abnormalities (e.g. fibroids, endometrial polyps)
- easily done, minimal cost, well-tolerated, sensitive and specific
- frequently avoids need for diagnostic hysteroscopy



Check for STIs before performing SHG and HSG to prevent PID in high-risk individuals. Consider pre-treatment with doxycycline.

#### Hysterosalpingography (HSG)

- x-ray contrast introduced through the cervix into the uterus
- used for evaluation of size, shape, configuration of uterus, congenital uterine abnormalities, tubal patency, or obstruction
- useful for investigation of infertility
- often replaced by sonohysterogram with Echovist® to look at tubes



## Common Procedures

### Genital Tract Biopsy

#### Vulvar Biopsy

- performed under local anesthetic
- Keyes/punch biopsy
- hemostasis achieved with local pressure and Monsel's solution (ferric sulfate), silver nitrate or suture (rarely)

#### Vaginal Biopsy and Cervical Biopsy

- anesthetic not necessary
- punch biopsy or biopsy forceps
- hemostasis with Monsel's solution and pressure

#### Endometrial Biopsy

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cytotec®) if nulliparous or postmenopausal
- more invasive procedure (D&C) may be done in the office or operating room ± hysteroscopy

### Colposcopy



- diagnostic use
  - magnifies surface structures of the vulva, vagina, cervix and perianal region
  - 1% acetic acid wash applied to cervix dehydrates cells and reveals "acetowhite" areas that correspond to increased nucleus-to-cytoplasm ratio (abnormal)
  - allows biopsy of acetowhite lesions for early identification of dysplasia and cancer
- therapeutic use
  - cryotherapy: nitrous oxide or carbon dioxide freezes dysplastic lesions, genital warts
  - laser vaporization: used to treat dysplastic lesions of the exocervix and benign ectropion
  - loop electrosurgical excision procedure (LEEP): excision of transformation zone with the cervical lesion; provides a specimen for pathological examination

### Vacuum Aspiration

- procedure to empty the contents of the uterus through a plastic or metal cannula (thin tube) attached to a vacuum source

#### Indications

- termination of pregnancy in 1<sup>st</sup> trimester

#### Manual Vacuum Aspiration (≤10 wk gestation)

- source of vacuum: hand-held, portable aspirator
- anesthesia: local (paracervical block) in most cases
- can be performed in an office setting
- suction curette connected to aspirator empties the uterus

#### Electric Vacuum Aspiration (≤13 wk gestation)

- source of vacuum: electric pump
- anesthesia: local (paracervical block) and conscious sedation or general anesthetic
- dilatation of cervix with dilators of increasing diameter
- suction curette connected to electric pump empties the uterus
- after aspiration, uterine cavity can be gently explored with sharp curette

#### Complications

- bleeding
- infection
- perforation of uterus, laceration of cervix
  - reduce risk with preprocedural cervical dilatation (misoprostol or osmotic dilators)
- retained products of conception
  - requires reaspiration, rare (2/1000)



## Dilatation and Curettage (D&C)

- determine depth with uterine sound prior to procedure
- dilatation of cervix with dilators of increasing diameter
- scrape entire uterine cavity with sharp curette
- anesthesia: general or local

### Indications

- diagnostic (rarely done without hysteroscopy)
  - abnormal uterine bleeding (AUB)
  - dysfunctional uterine bleeding (DUB)
- therapeutic
  - removal of retained products of conception following abortion
  - termination of pregnancy in 1st trimester
  - removal of small uterine polyps or pedunculated submucosal fibroids

### Complications

- bleeding
- infection
- perforation of uterus, laceration of cervix
  - reduce risk with preoperative misoprostol (Cytotec®) inserted per vagina to soften cervix and stimulate uterine contraction
- incompetent cervix – extremely rare
- Asherman's syndrome

## Laparoscopy



- laparoscope (fibre optic camera) used to view pelvic/abdominal contents through small incisions

### Indications

- diagnostic
  - evaluation of infertility, pelvic pain, pelvic masses, congenital anomalies, hemoperitoneum and endometriosis
- therapeutic
  - tubal ligation
  - lysis of adhesions
  - excision of ectopic pregnancy
  - excision/ablation of endometriosis
  - retrieval of lost IUDs
  - cystectomy, salpingo-oophorectomy and hysterectomy
  - myomectomy
  - treatment of stress urinary incontinence

### Contraindications

- bowel obstruction
- large hemoperitoneum
- clinically unstable patient
- inability to maintain pneumoperitoneum
- multiple previous abdominal surgeries (i.e. adhesions)

### Complications

- general anesthesia related
- insufflation of the preperitoneal abdominal wall
- injury to surrounding structures (e.g. aorta, inferior epigastric vessels, bowel, bladder, ureters)
- may need to convert to laparotomy
- infection

## Hysteroscopy

- flexible or rigid scope inserted through cervix into uterus to visualize uterine cavity
- distension medium is used to allow inspection of this potential space

### Indications

- diagnostic
  - detection of uterine anomalies or pathology (e.g. infertility work-up)
  - AUB
  - DUB
- therapeutic
  - removal of uterine polyps, fibroids, adhesions, septa
  - endometrial ablation

**Complications**

- perforation of uterus, laceration of cervix
- bleeding
- infection
- absorption of excess distension medium (when sugar solutions utilized, e.g. glucose, mannitol)
  - fluid overload, hyponatremia
  - procedure should be abandoned if the fluid deficit rises to 1 L; consider stopping at 500 cc
- air emboli
- anaphylactic shock

## Endometrial Ablation

- alternative invasive procedure to hysterectomy for treatment of AUB; performed as outpatient
- rationale is to coagulate or resect the endometrium basalis layer to prevent monthly build-up and reduce menstrual losses

**Methods**

- rollerball electrode coagulation or resection
- microwave endometrial ablation
- thermoablation (hot water), balloon ablation
- laser photocoagulation

**Complications**

- infection
- injury to pelvic viscera if uterus perforated
- hematometra
- absorption of excess distention medium → fluid overload, hyponatremia
- failure (i.e. bleeding/menorrhagia persists)
- recurrence of symptoms (~20% at 5 yr), may eventually require hysterectomy

## Hysterectomy

**Indications**

- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

**Complications**

- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

**Approaches**

1. vaginal vs. abdominal
  - indications for vaginal approach: mobile uterus, uterine size <12 wk
  - advantages of vaginal approach: less pain, faster recovery time, allows for simultaneous repair of rectocele/cystocele/enterocele, improved aesthetics
2. open vs. laparoscopic-assisted
  - advantages of laparoscopy: less pain, faster recovery, improved aesthetics, shorter hospital stay
3. robotic
  - similar advantages to laparoscopy
  - more dexterous

**Approaches to Hysterectomy**

- Abdominal hysterectomy: uterus removed via transverse or vertical laparotomy
- Vaginal hysterectomy: uterus removed via vagina. No visualization or entry into abdomen unless laparoscopic-assisted
- Laparoscopic/Robotic: uterus removed via vagina or morcellation

Table 1. Classification of Hysterectomy

Classification	Tissues Removed	Indications
Subtotal hysterectomy	Uterus	Inaccessible cervix (e.g. adhesions) Patient choice/preference
Total hysterectomy (extrafascial simple hysterectomy/type 1)	Uterus, cervix, uterine artery ligated at uterus	Uterine fibroids Endometriosis Adenomyosis Menorrhagia DUB
Total hysterectomy (extrafascial simple hysterectomy/type 1) + bilateral salpingo-oophorectomy (TAH/BSO)	Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries	Endometrial cancer Malignant adnexal masses >45 yr old Consider for endometriosis
Modified radical hysterectomy (type 2)	Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterosacral ligaments and upper 1-2 cm vagina	Cervical cancer (up to stage IBI, see Table 24)
Radical hysterectomy (type 3)	Uterus, cervix, upper 1/3-1/2 vagina, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum)	Cervical cancer

## Disorders of Menstruation



### Amenorrhea

#### Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

With Secondary Sexual Development		Without Secondary Sexual Development	
<i>Normal breast and pelvic development</i>	<i>Normal breast, abnormal uterine development</i>	<i>High FSH (hypergonadotropic hypogonadism)</i>	<i>Low FSH (hypogonadotropic hypogonadism)</i>
Hypothyroidism Hyperprolactinemia PCOS Hypothalamic dysfunction	Androgen insensitivity Anatomic abnormalities • Müllerian agenesis, uterovaginal septum, imperforate hymen	Gonadal dysgenesis • Abnormal sex chromosome (Turner's XO) • Normal sex chromosome (46XX, 46XY)	Constitutional delay (most common) Congenital abnormalities • Isolated GnRH deficiency • Pituitary failure (Kallman syndrome, head injury, pituitary adenoma, etc.) Acquired • Endocrine disorders (T1DM) • Pituitary tumors • Systemic disorders (IBD, JRA, chronic infections, etc.)

Table 3. Differential Diagnosis of Secondary Amenorrhea

With Hyperandrogenism	Without Hyperandrogenism
PCOS Autonomous hyperandrogenism (androgen secretion independent of the HPO axis) • Ovarian: tumour, hyperthecosis • Adrenal androgen-secreting tumour Late onset or mild congenital adrenal hyperplasia (rare)	Hypergonadotropic hypogonadism (aka premature ovarian failure: high FSH, low estradiol) • Idiopathic • Autoimmune: T1DM, autoimmune thyroid disease, Addison's disease • Iatrogenic: cyclophosphamide drugs, radiation Hyperprolactinemia Endocrinopathies: most commonly hyper or hypothyroidism Hypogonadotropic hypogonadism (low FSH): • Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan's syndrome Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia)



#### Primary Amenorrhea

No menses by age 14 in absence of 2° sexual characteristics or no menses by age 16 with 2° sexual characteristics.

#### Secondary Amenorrhea

No menses for >6 mo or 3 cycles after documented menarche.

#### Oligomenorrhea

Episodic vaginal bleeding occurring at intervals >35 d.



#### Prolactinoma Symptoms

Galactorrhea, visual changes, headache.



2° amenorrhea is pregnancy until proven otherwise.



Functional hypothalamic amenorrhea is the most common cause of amenorrhea.

## Investigations

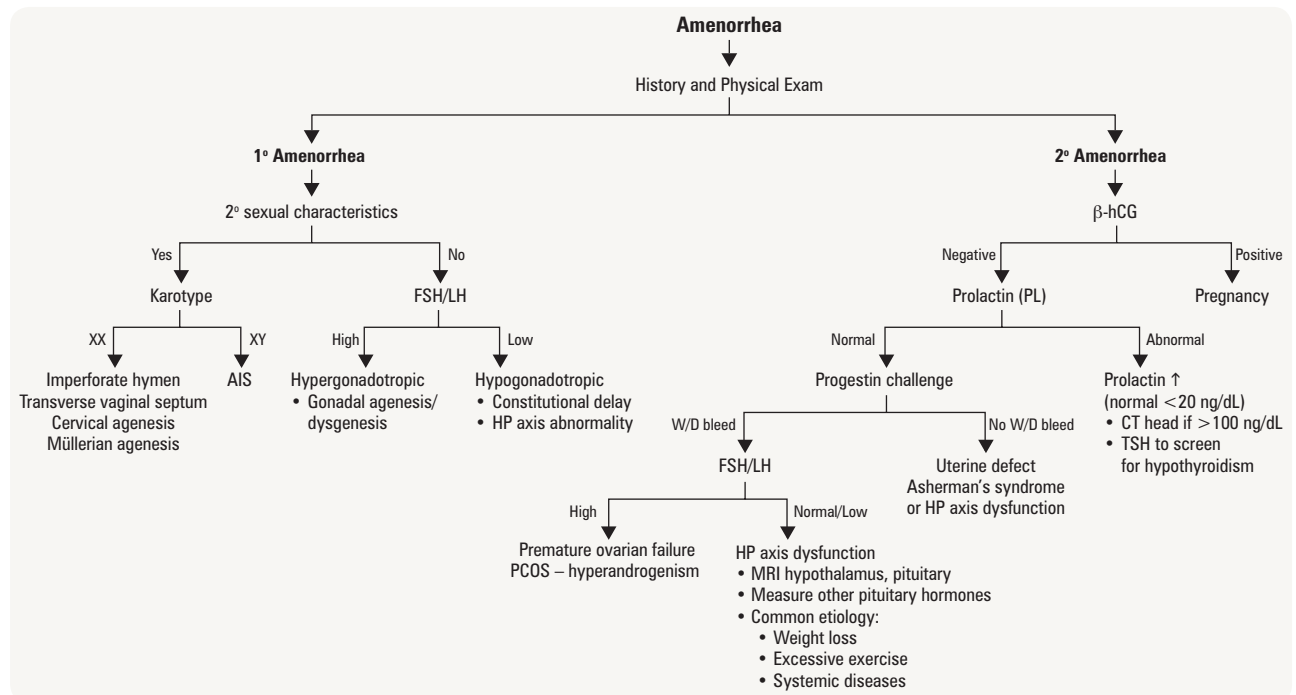


Figure 9. Diagnostic approach to amenorrhea

- $\beta$ -hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
  - medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10-14 d
  - any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive test/withdrawal bleed
    - ♦ withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progesterone results in bleeding
    - ♦ if no bleeding occurs, there may be inadequate estrogen (hypoestrogenism) or excessive androgens
- karyotype: indicated if premature ovarian failure or absent puberty
- U/S to confirm normal anatomy, identify PCOS

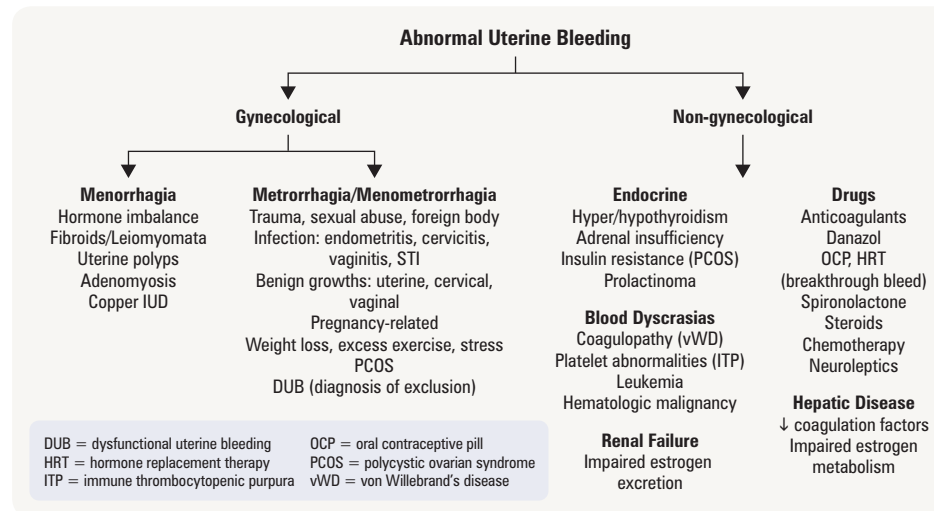
## Treatment

Table 4. Management of Amenorrhea

Etiology	Management
<b>1° AMENORRHEA</b>	
AIS	<ul style="list-style-type: none"> <li>• Gonadal resection after puberty</li> <li>• Psychological counselling</li> <li>• Creation of neo-vagina</li> </ul>
Anatomical <ul style="list-style-type: none"> <li>• Imperforate hymen</li> <li>• Transverse vaginal septum</li> <li>• Cervical agenesis</li> </ul>	<ul style="list-style-type: none"> <li>• Surgical management</li> </ul>
Müllerian dysgenesis (MRKH syndrome)	<ul style="list-style-type: none"> <li>• Psychological counselling</li> <li>• Creation of neo-vagina with dilation</li> <li>• Diagnostic study to confirm normal urinary system and spine</li> </ul>
<b>2° AMENORRHEA</b>	
Uterine defect <ul style="list-style-type: none"> <li>• Asherman's syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Evaluation with hysterosalpingography or sonohysterography</li> <li>• Hysteroscopy: excision of synechiae</li> </ul>
HP-axis dysfunction	<ul style="list-style-type: none"> <li>• Identify modifiable underlying cause</li> <li>• Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development</li> </ul>
Premature ovarian failure	<ul style="list-style-type: none"> <li>• Screen for diabetes mellitus, hypothyroidism, hypoparathyroidism, hypocortisolism</li> <li>• Hormonal therapy with estrogen + progestin to decrease risk of osteoporosis. Can use OCP</li> </ul>
Hyperprolactinemia	<ul style="list-style-type: none"> <li>• MRI/CT head to r/o lesion</li> <li>• If no demonstrable lesions by MRI:               <ul style="list-style-type: none"> <li>• Bromocriptine, cabergoline if fertility desired</li> <li>• Combined OCPs if no fertility desired</li> </ul> </li> <li>• Demonstrable lesions by MRI: surgical management</li> </ul>
Polycystic ovarian syndrome	



**Abnormal Uterine Bleeding**  
Change in frequency, duration or amount of menstrual flow.



**Figure 10. Approach to abnormal uterine bleeding**

**Table 5. Comparison of Anovulatory and Ovulatory Abnormal Uterine Bleeding**

	Anovulatory	Ovulatory
<b>Incidence</b>	90%	10%
<b>Definition</b>	Unpredictable endometrial bleeding of variable flow and duration; sex steroids are produced but not cyclically, resulting in irregular bleeding	Typically cyclic, but heavy or prolonged
<b>Etiology</b>	PCOS Thyroid dysfunction Elevated prolactin levels Rare estrogen-producing tumours Stress, weight loss, exercise Liver and kidney disease	Anatomic or physical lesion (e.g. polyp, fibroid, adenomyosis, neoplasm, foreign body) Hemostatic defect Infection; trauma Local disturbances in prostaglandins (elevated endomyometrial vasodilatory prostaglandin, decreased vasoconstrictive prostaglandin)
<b>Pathophysiology</b>	Estrogen-dependent breakthrough bleeding: chronic estrogen production unopposed by adequate progesterone production → continued proliferation of the endometrium → thickened endometrium outgrows its blood supply → focal necrosis with partial shedding not uniformly → bleeding is usually irregular, prolonged, and heavy	Depends on underlying etiology

### Investigations

- CBC, serum ferritin
- $\beta$ -hCG
- TSH, free  $T_4$
- coagulation profile (especially in adolescents): rule out von Willebrand's disease
- prolactin if amenorrheic
- FSH, LH
- serum androgens (especially free testosterone)
- day 21 (luteal phase) progesterone to confirm ovulation
- Pap test
- pelvic U/S: detect polyps, fibroids; measure endometrial thickness (postmenopausal)
- SHG: very sensitive for intrauterine pathology (polyps, submucous fibroids)
- HSG
- endometrial biopsy: consider biopsy in women >40 yr
  - must do endometrial biopsy in all women presenting with postmenopausal bleeding to exclude endometrial cancer
- D&C: not for treatment; diagnosis only (usually with hysteroscopy)

## Treatment

- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider dysfunctional uterine bleeding (DUB)
- medical
  - mild DUB (see sidebar)
    - ♦ NSAIDs
    - ♦ anti-fibrinolytic (e.g. Cyklokapron®) at time of menses
    - ♦ combined OCP
    - ♦ progestins (Provera®) on first 10-14 d of each month if oligomenorrheic
    - ♦ Mirena® IUD
    - ♦ danazol
  - acute, severe DUB
    - ♦ replace fluid losses, consider admission
    - ♦ a) estrogen (Premarin®) 25 mg IV q4h x 24h with Graval® 50 mg IV/PO q4h
    - ♦ b) Ovral®, or any OCP with minimum 50 µg estradiol 1 tab PO q4h x 24 h with Graval® 50 mg IV/PO q4h
      - taper Ovral® to 1 tab tid x 2 d → bid x 2 d → OD
    - ♦ after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
  - clomiphene citrate
    - ♦ consider in patients who are anovulatory and who wish to get pregnant
- surgical
  - endometrial ablation; consider pretreatment with danazol or GnRH agonists
    - ♦ if finished childbearing
    - ♦ repeat procedure may be required if symptom reoccurs
  - hysterectomy: definitive treatment



### Dysfunctional Uterine Bleeding

Abnormal bleeding not attributable to organic (anatomic/systemic) disease. DUB is a diagnosis of exclusion. Anovulatory AUB often used synonymously with DUB.

## Dysmenorrhea

### Etiology

- see *Differential Diagnoses of Common Presentations*, GY6

**Table 6. Comparison of Primary and Secondary Dysmenorrhea**

	Primary Dysmenorrhea	Secondary Dysmenorrhea
<b>Features</b>	Menstrual pain in absence of organic disease Begins 6 mo-2 yr after menarche (once ovulatory cycles established)	Menstrual pain due to organic disease Usually begins in women who are in their 20s, worsens with age May improve temporarily after childbirth
<b>Signs and Symptoms</b>	Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: nausea, vomiting, altered bowel habits, headaches, fatigue (prostaglandin-associated)	Associated dyspareunia, abnormal bleeding, infertility
<b>Diagnosis</b>	Associated dyspareunia, abnormal bleeding, infertility Rule out underlying pelvic pathology and confirm cyclic nature of pain	Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women <20 yr) U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis
<b>Treatment</b>	PG synthetase inhibitors (e.g. Anaprox®): should be started before onset of pain OCP: suppress ovulation/reduce menstrual flow	Treat underlying cause



### Primary Dysmenorrhea

Menstrual pain in absence of organic disease.

### Secondary Dysmenorrhea

Menstrual pain due to organic disease.



# Endometriosis



## Etiology

- not fully understood
- proposed mechanisms (combination likely involved)
  - retrograde menstruation (Sampson's theory)
    - ♦ seeding of endometrial cells by transtubal regurgitation during menstruation
    - ♦ endometrial cells most often found in dependent sites of the pelvis
  - immunologic theory: altered immunity may limit clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
    - ♦ undefined endogenous biochemical factor may induce undifferentiated peritoneal cells to develop into endometrial tissue
  - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - ♦ e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

## Epidemiology

- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 yr
- regresses after menopause

## Risk Factors

- family history (7-10 fold increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – resolve with treatment of anomaly
- nulliparity
- age >25 yr

## Sites of Occurrence

- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicoperitoneal fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs

## Clinical Features

- may be asymptomatic
- history
  - menstrual symptoms
    - ♦ cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
    - ♦ secondary dysmenorrhea
    - ♦ sacral backache with menses
    - ♦ pain may eventually become chronic, worsening perimenstrually
    - ♦ premenstrual and postmenstrual spotting
    - ♦ deep dyspareunia
  - infertility
    - ♦ 30-40% of patients with endometriosis will be infertile
    - ♦ 15-30% of those who are infertile will have endometriosis
  - bowel and bladder symptoms
    - ♦ frequency, dysuria, hematuria
    - ♦ diarrhea, constipation, hematochezia, dyschezia
- physical
  - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
  - fixed retroversion of uterus
  - firm, fixed adnexal mass (endometrioma)
  - physical findings not present in adolescent population

## Investigations

- definitive diagnosis requires:
  - direct visualization of lesions typical of endometriosis at laparoscopy
  - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)
- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - "powder-burn" lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
- CA-125
  - may be elevated in patients with endometriosis



### Endometriosis

The presence of endometrial tissue (glands and stroma) outside of the uterine cavity.



### Differential Diagnoses

- Chronic PID, recurrent acute salpingitis
- Hemorrhagic corpus luteum
- Benign/malignant ovarian neoplasm
- Ectopic pregnancy



### Endometrioma

Endometriotic cyst on surface of ovary.



There may be little correlation between the extent of endometriosis and symptomatology.



### Classic Triad of Endometriosis

- Dysmenorrhea
- Dyspareunia (cul de sac, uterosacral ligament)
- Dyschezia (uterosacral ligament, cul-de-sac, rectosigmoid attachment)



A sharp, firm, and exquisitely tender "barb" on the uterosacral ligament is a classic feature of endometriosis.

### Treatment

- depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility and impact to GI/GU systems (e.g. intestinal obstruction)
- medical
  - NSAIDs (e.g. naproxen sodium – Anaprox®)
  - pseudopregnancy
    - ♦ cyclic/continuous estrogen-progestin (OCP)
    - ♦ medroxyprogesterone (Depo-Provera®)
    - ♦ dienogest (Visanne®)
  - pseudomenopause
    - ♦ 2nd line: only short-term (<6 mo) due to osteoporotic potential with prolonged use, unless combined with add-back therapy (e.g. estrogen/progesterone or SERM). If long-term use required, add-back estrogen+progesterone
    - ♦ danazol (Danocrine®): weak androgen
      - side effects: weight gain, fluid retention, acne, hirsutism, voice change
    - ♦ leuprolide (Lupron®): GnRH agonist (suppresses pituitary)
      - side effects: hot flashes, vaginal dryness, reduced libido
      - can use ≥12 mo with add-back progestin or estrogen
- surgical
  - conservative laparoscopy using laser, electrocautery ± laparotomy
    - ♦ ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  - definitive: bilateral salpingo-oophorectomy ± hysterectomy
  - ± follow-up with medical treatment for pain control not shown to impact on preservation of fertility
  - best time to become pregnant is immediately after conservative surgery



Endometriosis is classified according to a scoring system standardized by the American Society for Reproductive Medicine. Score is based on location and extent of disease.



#### Recurrence Rates

Medical therapy: 30-50%  
Conservative surgery: 14-40%

## Adenomyosis

- synonym: “endometriosis interna” (uterine wall may be diffusely involved)

### Epidemiology

- 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

### Clinical Features

- often asymptomatic
- menorrhagia, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm, mobility not restricted, no associated adnexal pathology
- Halban sign: tender, softened uterus on premenstrual bimanual exam

### Investigations

- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

### Treatment

- iron supplements as necessary
- analgesics, NSAIDs
- OCP, medroxyprogesterone (Depo-Provera®)
- low dose danazol 100-200 mg PO OD (trial x 4 mo)
- GnRH agonists (e.g. leuprolide)
- definitive: hysterectomy (no conservative surgical treatment)



#### Adenomyosis

Extension of areas of endometrial glands and stroma into the myometrium.



Final diagnosis of adenomyosis is based on pathologic findings, but predictably identified on MRI.



#### Leiomyomata/Fibroids

Benign smooth muscle tumour of the uterus (most common gynecological tumour).

## Leiomyomata (Fibroids)



### Epidemiology

- diagnosed in approximately 40-50% of pre-menopausal women >35 yr
- more common in African Americans, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential (1:1000)
- typically regress after menopause; enlarging fibroids in a postmenopausal woman should prompt consideration of malignancy
  - 50% of leiomyosarcomas originate from within fibroids



Submucosal leiomyomata are most symptomatic (bleeding, infertility).



AUB in women >40 yr requires an endometrial biopsy to r/o cancer even if known to have fibroids.

### Pathogenesis

- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumour outgrows blood supply)
  - hyaline degeneration (most common degenerative change)
  - cystic degeneration (from breakdown of hyaline)
  - red/carneous degeneration (hemorrhage into tumour, may occur in pregnancy)
  - fatty degeneration
  - calcification
  - sarcomatous degeneration (rare)
- parasitic myoma: tumour becomes attached to another organ (typically omentum or small bowel mesentery), develops new blood supply and loses connection to uterus

### Clinical Features

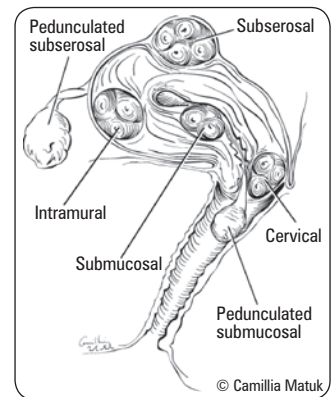
- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, menorrhagia
- pressure/bulk symptoms (20-50%)
  - pelvic pressure/heaviness
  - increased abdominal girth
  - urinary frequency and urgency
  - acute urinary retention (extremely rare but surgical emergency!)
  - constipation, bloating (rare)
- acute pelvic pain
  - fibroid degeneration
  - fibroid torsion (pedunculated subserosal)
- infertility, recurrent pregnancy loss
- pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)

### Investigations

- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or if intracavitary growth
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 yr)
- occasionally MRI is used for pre-op planning (e.g. before myomectomy)

### Treatment

- only if symptomatic, rapidly enlarging, if menorrhagia or menometrorrhagia, if intracavitary
- treat anemia if present
- conservative approach (watch and wait) if:
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron®)
  - OCP/Depo-Provera®
  - GnRH agonist: leuprolide (Lupron®), danazol (Danocrine®)
    - ♦ short-term use only (6 mo)
    - ♦ often used pre-myomectomy or pre-hysterectomy to reduce fibroid size
    - ♦ reduced bleeding
  - ulipristal acetate: a partial progesterone receptor agonist
- interventional radiology approach
  - uterine artery embolization (occludes both uterine arteries) → shrinks fibroids by 50% at 6 mo; improves menorrhagia in 90% of patients within 1-2 mo; not an option in women considering childbearing
- surgical approach
  - myomectomy (hysteroscopic, transabdominal or laparoscopic): preserves fertility
  - hysteroscopic resection of fibroid and endometrial ablation for menorrhagia
  - hysterectomy (see *Hysterectomy*, GY11)
  - note: avoid operating on fibroids during pregnancy (due to ↑ vascularity and potential pregnancy loss); expectant management usually best



**Figure 11. Possible anatomic locations of uterine leiomyomata**



The effect of pregnancy on fibroid size is variable.



#### Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids

NEJM 2012;366:421-432

**Study:** Phase III, double-blind RCT of the efficacy and side-effect profile of ulipristal acetate versus those of leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery.

**Outcomes:** Control of uterine bleeding at week 13 was the primary outcome. Secondary outcomes included bleeding pattern, amenorrhea, changes in fibroid/uterine volume, and global pain score.

**Patients:** 307 premenopausal women with symptomatic fibroids and excessive uterine bleeding were randomly assigned to oral ulipristal acetate (5 mg or 10 mg) or intramuscular injections of leuprolide acetate.

**Results:** Control of bleeding at week 13 was not significantly different between the treatment groups. All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group (47% reduction) than in the ulipristal groups (20-22%). 40% of the leuprolide group reported moderate-to-severe hot flashes, but only 11% (5 mg) and 10% (10 mg) of the ulipristal groups did.

**Conclusions:** Oral ulipristal acetate (5 mg or 10 mg) is noninferior to intramuscular leuprolide acetate for control of uterine bleeding due to fibroids, and it had a better side-effect profile.



#### Suppression of Ovarian Activity with a Drospirenone-Containing Oral Contraceptive in a 24/4 Regimen

Contraception 2008;78:16-25

**Study:** Double-blind randomized.

**Patients:** Women aged 18-35 yr, post-ovulation or had a follicular diameter ≥15 mm before day 23 during a pre-treatment cycle.

**Intervention:** Drospirenone 3 mg plus ethinyl estradiol 20 µg administered in 24/4 regimen vs. 21/7 regimen.

**Outcome:** Suppression of ovarian activity (Hoogland score).

**Results:** Women on a 24/4 regimen had greater and more consistent ovarian suppression than the 21/7 group. More women in the 24/4 group had no ovarian activity compared to women in the 21/7 group.

**Conclusion:** A 24/4 regimen is associated with greater ovarian suppression than a 21/7 regimen.

# Contraception

- see [Family Medicine](#), FM20

**Table 7. Classification of Contraceptive Methods**

Type	Effectiveness (perfect use, typical use)
<b>Physiological</b>	
Withdrawal/coitus interruptus	77%
Rhythm method/calendar/mucus/symptothermal	98%, 76%
Lactational amenorrhea	98% (first 6 mo postpartum)
Chance – no method used	10%
Abstinence of all sexual activity	100%
<b>Barrier Methods</b>	
Condom alone	98%, 85%
Spermicide alone	82%, 71%
Sponge – Parous	80%, 68%
– Nulliparous	91%, 84%
Diaphragm with spermicide	94%, 84%
Female condom	95%, 79%
Cervical cap – Parous	74%, 68%
– Nulliparous	91%, 84%
<b>Hormonal</b>	
OCP	99.7%, 92%
Nuva Ring®	99.7%, 92%
Transdermal (Ortho Evra®)	99.7%, 92%
Depo-Provera®	99.7%, 97%
Progestin-only pill (Micronor®)	90-99%
Mirena® IUD	99.9%
<b>Copper IUD</b>	99.3%
<b>Surgical</b>	
Tubal ligation	99.65%
Vasectomy	99.9%
<b>Emergency Postcoital Contraception (EPC)</b>	
Yuzpe® method	98% (within 24 h), decreases by 30% at 72 h
“Plan B” levonorgestrel only	98% (within 24 h), decreases by 70% at 72 h
Postcoital IUD	99.9%

Effectiveness: percentage of women reporting no pregnancy after 1 yr of use.

## Hormonal Methods

### Combined Oral Contraceptive Pills (OCPs)

- most contain low dose ethinyl estradiol (20-35 µg) plus progestin (norethindrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

### Transdermal (Ortho Evra®)

- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive weeks (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

### Contraceptive Ring (Nuva Ring®)

- thin flexible plastic ring; releases etonogestrel 120 µg/d and estradiol 15 µg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- avoids first pass effect
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

### Starting Hormonal Contraceptives

- thorough history and physical examination, including blood pressure and breast exam
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam can be delayed until a subsequent visit



### Counselling the Adolescent about Contraception

More than 90% of adolescent pregnancies are unintended, and ~50% of all pregnancies occur within the first 6 mo of initiating sexual activity. In addition, 85% of sexually active women become pregnant within 1 yr if no contraception is used and even some of the least effective contraceptive methods markedly decrease the risk of pregnancy.



### Oral Contraceptives and the Risk of Venous Thromboembolism: An Update (2010)

*J Obstet Gyn Canada* 2010;32:1192-1197

#### Rates of venous thromboembolism

(VTE: DVT and PE) expressed in women/yr  
 Non-users of reproductive age 4-5/10 000  
 Oral contraceptive (OCP) users\* 9-10/10 000  
 Pregnancy 29/10 000  
 Immediate post-partum 300-400/10 000  
 \* Risk is highest in the first months of use and in medication switch.

#### Effect of ethinyl estradiol dose

ALL OCPs with ≤35 µg ethinyl estradiol carry a lower risk of VTE compared with oral contraceptives with 50 µg.

#### Effect of progestin type

*Drospirenone*: third generation progestin, e.g. Yasmin® and Yaz®  
*Levonorgestrel*: second generation progestin, e.g. Alesse®

Two high quality research studies found comparable VTE rates with drospirenone-containing OCPs and other approved products.

1. Dinger et al., *Contraception* 2007;75:344-354
2. Seeger et al., *Obstet Gynecol* 2007;110:587-593

Two reports with significant methodological flaws found increased VTE risk. Results and conclusions may have been distorted by residual confounding.

1. Lidegaard et al., *BMJ* 2009;339:b2890
2. Van Hylckama Vlieg et al., *BMJ* 2009;339:b2921

#### Conclusion

- Occurrence of serious risks, such as VTE, is rare with all contemporary OCPs.
- Individualized risk assessment is mandatory.
- For most healthy women of reproductive age, the benefits of OCPs will outweigh the risks.



### Risk of Non-Fatal Venous Thromboembolism in Women Using Oral Contraceptives Containing Drospirenone Compared with Women Using Oral Contraceptives Containing Levonorgestrel: A Case-Control Study Using United States Claims Data

*BMJ* 2011;342:d2151

**Study:** Nested case-control and cohort study. Patients: Women aged 15-44 yr receiving oral contraceptives.

**Intervention:** Drospirenone-containing contraceptive vs. Levonorgestrel-containing contraceptive.

**Outcome:** Non-fatal venous thromboembolism.

**Results:** Women receiving drospirenone-containing oral contraceptives were two times as likely to develop non-fatal VTE compared to women receiving levonorgestrel-containing contraceptives (age adjusted incidence rate ratio was 2.8).

**Table 8. Combined Estrogen and Progestin Contraceptive Methods**

Mechanism of Action	Advantages	Side Effects	Contraindications
<ul style="list-style-type: none"> <li>Ovulatory suppression through inhibition of LH and FSH</li> <li>Decidualization of endometrium</li> <li>Thickening of cervical mucus resulting in decreased sperm penetration</li> </ul>	<ul style="list-style-type: none"> <li>Highly effective</li> <li>Reversible</li> <li>Cycle regulation</li> <li>Decreased dysmenorrhea and menorrhagia (less anemia)</li> <li>Decreased benign breast disease and ovarian cyst development</li> <li>Decreased risk of ovarian and endometrial cancer</li> <li>Increased cervical mucus which may lower risk of STIs</li> <li>Decreased PMS symptoms</li> <li>Improved acne</li> <li>Osteoporosis protection (possibly)</li> </ul>	<p><b>Estrogen-related</b></p> <ul style="list-style-type: none"> <li>Nausea</li> <li>Breast changes (tenderness, enlargement)</li> <li>Fluid retention/bloating/edema</li> <li>Weight gain (rare)</li> <li>Migraine, headaches</li> <li>Thromboembolic events</li> <li>Liver adenoma (rare)</li> <li>Breakthrough bleeding (low estradiol levels)</li> </ul> <p><b>Progestin-related</b></p> <ul style="list-style-type: none"> <li>Amenorrhea/breakthrough bleeding</li> <li>Headaches</li> <li>Breast tenderness</li> <li>Increased appetite</li> <li>Decreased libido</li> <li>Mood changes</li> <li>Hypertension</li> <li>Acne/oily skin*</li> <li>Hirsutism*</li> </ul> <p>* Androgenic side effects may be minimized by prescribing formulations containing desogestrel, norgestimate, drospirenone or cyproterone acetate</p>	<p><b>Absolute</b></p> <ul style="list-style-type: none"> <li>Known/suspected pregnancy</li> <li>Undiagnosed abnormal vaginal bleeding</li> <li>Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C, S or antithrombin III deficiency), active thrombophlebitis</li> <li>Cerebrovascular or coronary artery disease</li> <li>Estrogen-dependent tumours (breast, uterus)</li> <li>Impaired liver function associated with acute liver disease</li> <li>Congenital hypertriglyceridemia</li> <li>Smoker age &gt;35 yr</li> <li>Migraines with focal neurological symptoms (excluding aura)</li> <li>Uncontrolled hypertension</li> </ul> <p><b>Relative</b></p> <ul style="list-style-type: none"> <li>Migraines (non-focal with aura &lt;1 h)</li> <li>Diabetes mellitus complicated by vascular disease</li> <li>SLE</li> <li>Controlled hypertension</li> <li>Hyperlipidemia</li> <li>Sickle cell anemia</li> <li>Gallbladder disease</li> </ul> <p><b>Drug Interactions/Risks</b></p> <ul style="list-style-type: none"> <li>Rifampin, phenobarbital, phenytoin and primidone can decrease efficacy, requiring use of back-up method</li> <li>No evidence of fetal abnormalities if conceived on OCP</li> <li>No evidence that OCP is harmful to nursing infant but may decrease milk production. Not recommended until 6 wk postpartum, ideally until 3 mo postpartum</li> </ul>

Reference: World Health Organization Guidelines for Oral Contraceptive Pill Use

**Table 9. Selected Examples of OCPs**

Type	Active Compounds (estriol and progestin derivative)	Advantages	Disadvantages
<b>Alesse®</b>	17 µg ethinyl estradiol and 0.5 mg levonorgestrel	<ul style="list-style-type: none"> <li>Low-dose therefore often a good starting OCP</li> <li>Can improve acne and help regulate menstrual cycles</li> </ul>	<ul style="list-style-type: none"> <li>Low-dose pills can often result in breakthrough bleeding</li> <li>If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content</li> </ul>
<b>Tri-cyclen®</b>	35 µg ethinyl estradiol and 0.180/0.215/0.250 mg norgestimate Triphasic oral contraceptive (graduated levels of progesterone)	<ul style="list-style-type: none"> <li>Low androgenic activity can help with acne</li> </ul>	<ul style="list-style-type: none"> <li>Triphasic OCPs should not be used continuously (unlike monophasic formulations), although should be used continuously for 1 pack</li> </ul>
<b>Yasmin® and Yaz®</b>	<ul style="list-style-type: none"> <li>Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin)</li> <li>Yaz®: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4-d pill (4 d pill free interval)</li> <li>Drospirenone has antimineralocorticoid activity and antiandrogenic effects</li> </ul>	<ul style="list-style-type: none"> <li>Decreased perception of cyclic weight gain/bloating</li> <li>Fewer PMS symptoms</li> <li>Improved acne</li> </ul>	<ul style="list-style-type: none"> <li>Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency)</li> <li>Check potassium if patient also on ACE inhibitor, ARB, K<sup>+</sup>-sparing diuretic, heparin</li> <li>Continue use of spironolactone</li> <li>Increased risk of DVT-PE</li> </ul>



Irregular breakthrough bleeding often occurs in the first few months after starting OCP. Usually resolves after three cycles.

**Missed Combined OCPs**

Miss 1 pill in <24 h

- Take 1 pill ASAP, and the next pill at the usual time

Miss ≥1 pill in a row in first wk

- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Use back-up contraception for 7 d. EPC may be necessary

Miss <3 pills in 2nd or 3rd wk of cycle

- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack
- Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- No need for back-up contraception

Miss ≥3 pills during the 2nd or 3rd wk

- Take 1 pill ASAP, and continue taking one pill daily until the end of the pack.
- Don't take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
- Start the next pack immediately after finishing the previous one
- Use back-up contraception for 7 d. EPC may be necessary.

S. SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations.  
JOGC 2008;30:1050-1062. <http://www.sogc.org/guidelines/documents/gui219EC00811.pdf>

**PROGESTIN-ONLY METHOD****Table 10. Progestin Only Contraceptive Methods**

Indications	Mechanism of Action	Side Effects	Contraindications
<ul style="list-style-type: none"> <li>Suitable for postpartum women (does not affect breast milk supply)</li> <li>Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease)</li> <li>Women intolerant of estrogenic side effects of combined OCPs</li> </ul>	<ul style="list-style-type: none"> <li>Progestin prevents LH surge</li> <li>Thickening of cervical mucus</li> <li>Decrease tubal motility</li> <li>Endometrial decidualization</li> <li>Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs</li> </ul>	<ul style="list-style-type: none"> <li>Irregular menstrual bleeding</li> <li>Weight gain</li> <li>Headache</li> <li>Breast tenderness</li> <li>Mood changes</li> <li>Functional ovarian cysts</li> <li>Acne/oily skin</li> <li>Hirsutism</li> </ul>	<p><b>Absolute</b></p> <ul style="list-style-type: none"> <li>None</li> </ul>



## Selected Examples of Progestin-Only Methods

### Progestin-Only Pill ("minipill")

- Micronor® 0.35 mg norethindrone
- taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1-13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited in 60% of women; most have regular cycles (but may cause oligo/amenorrhea)
- highly effective if also post-partum breastfeeding, or if >35 yr

### Depo-Provera®

- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wk (convenient dosing)
- initiate within 5 d of beginning of normal menses, immediately postpartum in breastfeeding and non-breastfeeding women
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
- highly effective 99%; failure rate 0.3%
- side effect: decreased bone density (may be reversible)
- disadvantage: restoration of fertility may take up to 1-2 yr



### Missed Progestin-Only Pills >3 hours

Use back-up contraceptive method for at least 48 h. Continue to take remainder of pills as prescribed.

### Missed Depo-Provera

- If last injection given 13-14 wk prior: give next injection immediately
- if >14 wk prior, do  $\beta$ -hCG
  - If  $\beta$ -hCG is positive, give EPC and no injection
  - If  $\beta$ -hCG is negative, give next injection right away and:
    - Intercourse occurred in last 5 d: give EPC, use back-up contraception for 7 d. Repeat  $\beta$ -hCG in 3 wk
    - Intercourse occurred >5 d ago but within the last 14 d: use back-up contraception for 7 d. Repeat  $\beta$ -hCG in 3 wk
    - Intercourse occurred >14 d ago: use back-up contraception for 7 d
- No evidence of fetal abnormalities if conceived on DMPA

S. SOGC Committee Opinion on Missed Hormonal Contraceptives: New Recommendations.

JOGC 2008;30:1050-62. <http://www.sogc.org/guidelines/documents/gui219EC00811.pdf>



## Intrauterine Device (IUD)

Table 11. IUD Contraceptive Methods

Mechanism of Action	Side Effects	Contraindications
<ul style="list-style-type: none"> <li>• <b>Copper-containing IUD (Nova-T®):</b> mild foreign body reaction in endometrium toxic to sperm and alters sperm motility</li> <li>• <b>Progesterone-releasing IUD (Mirena®):</b> decidualization of endometrium and thickening of cervical mucus; minimal effect on ovulation</li> <li>• Highly effective (95-99%); failure rate 0-1.2%</li> <li>• Contraceptive effects last 5 yr</li> <li>• Reversible, private, convenient</li> <li>• May be used in women with contraindications to OCPs or wanting long-term contraception</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Both Copper and Progesterone IUD</b> <ul style="list-style-type: none"> <li>• Breakthrough bleeding</li> <li>• Expulsion (5% in the first year, greatest in first month and in nulliparous women)</li> <li>• Uterine wall perforation (1/1000) on insertion</li> <li>• If pregnancy occurs with an IUD, increased risk of ectopic</li> <li>• Increased risk of PID (within first 10 d of insertion only)</li> </ul> </li> <li>• <b>Copper IUD:</b> increased blood loss and duration of menses, dysmenorrhea</li> <li>• <b>Progesterone IUD:</b> bloating, headache</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Absolute</b> <ul style="list-style-type: none"> <li>• <b>Both Copper and Progesterone IUD</b> <ul style="list-style-type: none"> <li>• Known or suspected pregnancy</li> <li>• Undiagnosed genital tract bleeding</li> <li>• Acute or chronic PID</li> <li>• Lifestyle risk for STIs*</li> </ul> </li> <li>• <b>Copper IUD:</b> <ul style="list-style-type: none"> <li>• Known allergy to copper</li> <li>• Wilson's disease</li> </ul> </li> </ul> </li> <li>• <b>Relative</b> <ul style="list-style-type: none"> <li>• <b>Both Copper and Progesterone IUD</b> <ul style="list-style-type: none"> <li>• Valvular heart disease</li> <li>• Past history of PID or ectopic pregnancy</li> <li>• Presence of prosthesis</li> <li>• Abnormalities of uterine cavity, intracavitary fibroids</li> <li>• Cervical stenosis</li> <li>• Immunosuppressed individuals (e.g. HIV)</li> </ul> </li> <li>• <b>Copper IUD:</b> severe dysmenorrhea or menorrhagia</li> </ul> </li> </ul>

\*Cervical swabs for gonorrhea and chlamydia should be done prior to IUD insertion



### Medroxyprogesterone (Depo-Provera®) and Bone Mineral Density Loss

CMAJ 2005;172:746

Extended use (up to 5 yr) of medroxyprogesterone acetate has been found to decrease spine and hip bone mineral density (BMD) by 4% to 6.9%. 2 yr after discontinuation, only partial recovery of BMD has been noted.



### Canadian Consensus Guideline on Continuous and Extended Hormonal Contraception

J Obstet Gyn Canada 2007;29:S1-S2

#### Definitions

- **Extended Use:** The use of combined hormonal contraceptives with planned hormone-free intervals.
- **Continuous Use:** Uninterrupted use of combined hormonal contraceptives without hormone-free intervals.

#### What can be used?

Oral, transdermal and vaginally administered combined hormonal contraceptives, including those originally designed for cyclic use, can be administered in a variety of Continuous and Extended (C/E) regimens.

#### Efficacy and Adherence

Continuous combined hormonal contraceptive regimens are as effective as cyclic regimens in preventing pregnancy. Use of C/E combined hormonal contraceptives may be more "forgiving" about missed doses because of the absence of a hormone-free interval.

#### Side Effects

The side effect profile of C/E combined hormonal contraceptive regimens is not worse than with cyclic regimens, and may even be improved.

#### Medical/Non-contraceptive Usage

For women in the perimenopausal transition who may be ovulating, C/E combined hormonal contraceptive is preferred to hormonal replacement therapy for controlling problematic bleeding and vasomotor symptoms.



### Assessing the Risk of Venous Thromboembolic Events in Women Taking Progestin-Only Contraception: A Meta-Analysis

BMJ 2012;345:e4944

Published online 2012 August 7. doi: 10.1136/bmj.e4944

**Study:** Systematic review and meta-analysis of RCTs and observational studies to see if there is an increased risk of VTE on progestin only OCP and if route of administration had any effect.

**Results:** They found 8 observational studies. Across all 8 studies, 147 women had VTEs. The adjusted relative risk of a VTE for users versus non-users of a progestin-only contraceptive was 1.03 (95% CI 0.76 to 1.39).

**Conclusion:** Oral and intrauterine route made no difference. The relative risk of a VTE for users of an injectable progestin versus non-users was 2.67 (1.29 to 5.53).



### New SOGC Recommendations for Depo-Provera® Users

- Inform patients of potential risks and benefits at intervals throughout course of treatment
- Recommend ways to improve bone health such as calcium, vitamin D, weight-bearing exercise, smoking cessation, decreased alcohol and caffeine intake
- There is no evidence to suggest routine BMD testing

SOGC News Release. New recommendations from national ob/gyn society address Depo-Provera®, bone loss. May 2006. [http://www.sogc.org/media/pdf/advisories/dmpa-may2006\\_e.pdf](http://www.sogc.org/media/pdf/advisories/dmpa-may2006_e.pdf)



## Emergency Postcoital Contraception (EPC)



**Table 12. Emergency Contraceptive Methods**

Method	Mechanism of Action	Side Effects	Contraindications
<b>HORMONAL</b>			
<b>Yuzpe Method</b> <ul style="list-style-type: none"> <li>Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d</li> <li>Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg/levonorgestrel 500 µg)</li> <li>Can substitute with any OCP as long as same dose of estrogen used</li> <li>2% overall risk of pregnancy</li> <li>Efficacy decreased with time (e.g. less effective at 72 h than 24 h)</li> </ul>	<ul style="list-style-type: none"> <li>Unknown; theories include:               <ul style="list-style-type: none"> <li>Suppresses ovulation or causes deficient luteal phase</li> <li>Alters endometrium to prevent implantation</li> <li>Affects sperm/ova transport</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Nausea (due to estrogen; treat with Gravol®)</li> <li>Irregular spotting</li> </ul>	<ul style="list-style-type: none"> <li>Pre-existing pregnancy (although not teratogenic)</li> <li>Caution in women with contraindications to OCP (although NO absolute contraindications)</li> </ul>
<b>"Plan B"</b> <ul style="list-style-type: none"> <li>Consists of levonorgestrel 750 µg q12h for 2 doses (can also take 2 doses together); taken within 72 h of intercourse</li> <li>Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if &gt;24 h</li> <li>No estrogen thus very few contraindications/side effects (less nausea)</li> </ul>			
<b>NON-HORMONAL</b>			
<b>Postcoital IUD (Copper)</b> <ul style="list-style-type: none"> <li>Insert up to 7 d postcoitus</li> <li>Prevents implantation</li> <li>1% failure rate</li> <li>Can use for short duration in higher risk individuals</li> <li>Mirena® IUD cannot be used as EPC</li> </ul>	• See Table 11	• See Table 11	• See Table 11

### Follow-up

- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counseling



Any OCP can be used as EPC; 100 µg ethinyl estradiol PO q12h x 2 doses.

- Levonorgestrel emergency contraception regimens are more effective and cause fewer side effects than the Yuzpe regimen
- Levonorgestrel emergency contraception single dose (1.5 mg) and the 2-dose levonorgestrel regimen (0.75 mg 12 h apart) have similar efficacy with no difference in side effects

SOGC Clinical Practice Guidelines: Emergency Contraception. *JOGC* 2012;34:870-878.  
[http://www.sogc.org/guidelines/documents/gui280CPG1209E\\_000.pdf](http://www.sogc.org/guidelines/documents/gui280CPG1209E_000.pdf)



## Infertility

### Epidemiology

- 10-15% of couples
- must investigate both members of the couple

## Female Factors

### Etiology

- ovulatory dysfunction (15-20%)
  - hypothalamic (hypothalamic amenorrhea)
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - PCOS
    - premature ovarian failure
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, Cushing's syndrome, renal/hepatic failure)
  - congenital (Turner's syndrome, gonadal dysgenesis or gonadotropin deficiency)
  - stress, poor nutrition, excessive exercise (even with presence of menstruation)
- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - PID
    - adhesions (previous surgery, peritonitis, endometriosis)
    - ligation/occlusion (e.g. previous ectopic pregnancy)
  - uterine factors (<5%)
    - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure
    - intrauterine adhesions (e.g. Asherman's syndrome)
    - infection (endometritis, pelvic TB)
    - fibroids/polyps (particularly intrauterine)
    - endometrial ablation
  - cervical factors (5%)
    - hostile or acidic cervical mucus
    - anti-sperm antibodies
    - structural defects (cone biopsies, laser or cryotherapy)



**Infertility:** inability to conceive or carry to term a pregnancy after one year of regular, unprotected intercourse.

**Primary infertility:** infertility in the context of no prior pregnancies.

**Secondary infertility:** infertility in the context of a prior conception.

Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr.



### Requirements for Conception

- Ovary
- Tube
- Cervix
- Endometrium
- Sperm

- endometriosis (15-30%)
- multiple factors (30%), see GY22
- unknown factors (10-15%)

### Investigations

- ovulatory
  - day 3: FSH, LH, TSH, prolactin  $\pm$  DHEA, free testosterone (if hirsute)
  - day 21-23: serum progesterone to confirm ovulation
  - initiate basal body temperature monitoring (biphasic pattern)
  - postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
- tubal factors
  - HSG (can be therapeutic – opens fallopian tube)
  - SHG (can be therapeutic – opens fallopian tube)
  - laparoscopy with dye insufflation (or tubal dye test)
- peritoneal/uterine factors
  - HSG/SHG, hysteroscopy
- other
  - karyotype

### Treatment

- education: timing of intercourse in relation to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
- medical
  - ovulation induction
    - ♦ clomiphene citrate (Clomid<sup>®</sup>): estrogen antagonist that causes a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; causes increased FSH and LH, leading to ovulation induction (works much better if anovulatory)
    - ♦ human menopausal gonadotropin – HMG (Pergonal<sup>®</sup>), urofollitropin – FSH (Metrodin<sup>®</sup>) – FSH and LH extracted from urine of postmenopausal women
    - ♦ followed by  $\beta$ -hCG for stimulation of ovum release
  - may add
    - ♦ bromocriptine (dopamine agonist) if elevated prolactin
    - ♦ dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
    - ♦ metformin (for PCOS)
    - ♦ luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
    - ♦ ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
- surgical/procedural
  - tubuloplasty
  - lysis of adhesions
  - artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
  - sperm washing
  - IVF (in vitro fertilization)
  - IFT (intrafallopian transfer)
  - GIFT\* (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
  - ZIFT\* (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
  - TET\* (tubal embryo transfer): transfer after >24 h culture
  - ICSI (intracytoplasmic sperm injection)
  - IVM (in vitro maturation)
  - $\pm$  oocyte or sperm donors
  - $\pm$  pre-genetic screening for single gene defects in karyotype of zygote
  - \*Not performed in Canada



#### When Should Investigations Begin?

- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo
- >40 yr: immediately
- Earlier if:
  - History of PID
  - History of infertility in previous relationship
  - Prior pelvic surgery
  - Chemotherapy/radiation in either partner
  - Recurrent pregnancy loss
  - Moderate-severe endometriosis



#### Controversial and Evolving Ethical Issues

- Infertility demands non-judgmental discussion
- Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes and other advanced reproductive technologies are still evolving and remain controversial
- If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician



#### Summary of Current Legislation in Canada

##### Bill C-13 Assisted Human Reproduction Act 2004:

What is not allowed

- Cloning people
- Cloning stem cells
- Growing human embryos for research
- Sex selection
- Making changes to human DNA that would pass from one generation to the rest
- Creating people who have animal DNA
- Buying or selling embryos, sperm, eggs or other human reproductive material

What is allowed

- Surrogate mothers
- Donating sperm, eggs and other reproductive material
- Using embryos, sperm, eggs, etc., to assist conception
- Using human embryos and stem cells in research
- Sex selection in X-linked genetic diseases



#### Normal Semen Analysis (WHO lower reference limits)

- Must be obtained after 2-7 d of abstinence
  - Volume 1.5 cc
  - Count 15 million/cc
  - Vitality 58% live
  - Motility 32% progressive, 40% total (progressive + non-progressive)
  - Morphology 4.0% normal

## Male Factors

- see [Urology](#), U33



### Etiology

- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)

### Investigations

- semen analysis and culture
- post-coital (Huhner) test: rarely done

# Gynecological Infections



## Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 3.8-4.2
- smear contains epithelial cells, *Lactobacilli*
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

## Vulvovaginitis

### PREPUBERTAL VULVOVAGINITIS

- clinical features
  - irritation, pruritus
  - discharge
  - vulvar erythema
  - vaginal bleeding (specifically due to Group A *Streptococci* and *Shigella*)
- differential diagnosis
  - non-specific vulvovaginitis (25-75%)
  - infections (respiratory, enteric, systemic, sexually acquired)
  - foreign body (toilet paper most common)
  - *Candida* (if using diapers)
  - pinworms
  - polyps, tumour (ovarian malignancy)
  - vulvar skin disease (lichen sclerosis, condyloma acuminata)
  - trauma (accidental straddle injury, sexual abuse)
  - psychosomatic vaginal complaints (specific to vaginal discharge)
  - endocrine abnormalities (specific to vaginal bleeding)
  - blood dyscrasia (specific to vaginal bleeding)
- etiology
  - infectious:
    - ♦ poor hygiene, proximity of vagina to anus
    - ♦ recent infection (respiratory, enteric, systemic)
    - ♦ STI: investigate sexual abuse
  - nonspecific:
    - ♦ lack of protective hair and labial fat pads
    - ♦ lack of estrogenization
    - ♦ susceptible to chemicals, soaps (bubble baths), medications and clothing
    - ♦ enuresis
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified



#### Vulvovaginitis

Vulvar and vaginal inflammation.



Most common gynecological problem in prepubertal girls is non-specific vulvovaginitis, not yeast!



There is no high quality evidence showing a link between vulvovaginal candidiasis and hygienic habits or wearing tight or synthetic clothing.



#### Prepubertal and Adolescent Gynecological Infections: Legal Aspects of Confidentiality

- Clinicians who treat adolescents must be aware of federal, state and provincial laws related to adolescent consent and confidentiality
- They must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice

**Table 13. Other Common Causes of Vulvovaginitis in Prepubertal Girls**

	Pinworms	Lichen Sclerosis	Foreign Body
<b>Diagnosis</b>	Cellophane tape test	Area of white patches and thinning of skin	
<b>Treatment</b>	Empirical treatment with mebendazole	Topical steroid creams	Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia

**POSTMENOPAUSAL VAGINITIS/ATROPHIC VAGINITIS**

- clinical features
  - dyspareunia
  - post-coital spotting
  - mild pruritus
- investigations
  - atrophy is usually a visual diagnosis: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  - rule out malignancy: especially endometrial cancer
- treatment
  - local estrogen replacement (ideal): Premarin® cream, VagiFem® tablets, or Estring®
  - oral or transdermal hormone replacement therapy (if treatment for systemic symptoms is desired)
  - good hygiene

**INFECTIOUS VULVOVAGINITIS****Table 14. Infectious Vulvovaginitis**

	<b>Candidiasis (Moniliasis)</b>	<b>Bacterial Vaginosis (BV)</b>	<b>Trichomoniasis</b>
<b>Organisms</b>	<i>Candida albicans</i> (90%) <i>Candida glabrata</i> (<5%) <i>Candida tropicalis</i> (<5%)	<i>Gardnerella vaginalis</i> <i>Mycoplasma hominis</i> Anaerobes: <i>Prevotella</i> , <i>Mobiluncus</i> , <i>Bacteroides</i>	<i>Trichomonas vaginalis</i> (flagellated protozoan)
<b>Pathophysiology or Transmission</b>	Predisposing factors include: • Immunosuppressed host (diabetes, AIDS, etc.) • Recent antibiotic use • Increased estrogen levels (e.g. pregnancy, OCP)	Replacement of vaginal <i>Lactobacillus</i> with organisms above	Sexual transmission
<b>Discharge</b>	Whitish, "cottage cheese," minimal	Grey, thin, diffuse	Yellow-green, malodorous, diffuse, frothy
<b>Other</b>	• 20% asymptomatic	• 50-75% asymptomatic	• 25% asymptomatic
<b>Signs/Symptoms</b>	• Intense pruritus • Swollen, inflamed genitals • Vulvar burning, dysuria, dyspareunia	• Fishy odour, esp. after coitus • Absence of vulvar/vaginal irritation	• Petechiae on vagina and cervix • Occasionally irritated tender vulva • Dysuria, frequency
<b>pH</b>	≤4.5	≥4.5	≥4.5
<b>Saline Wetmount</b>	KOH wetmount reveals hyphae and spores	• >20% clue cells = squamous epithelial cells dotted with coccobacilli ( <i>Gardnerella</i> ) • Paucity of WBC • Paucity of <i>Lactobacilli</i> • Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)	• Motile flagellated organisms • Many WBC • Inflammatory cells (PMNs)
<b>Treatment</b>	• Clotrimazole, butoconazole, miconazole, terconazole suppositories and/or creams for 1, 3 or 7 d treatments • Treatment in pregnancy is usually topical • Fluconazole 150 mg PO in single dose (can be used in pregnancy)	• No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure • Oral • Metronidazole 500 mg PO bid x 7 d • Topical • Metronidazole gel 0.75% x 5 d OD (may be used in pregnancy) • Clindamycin 2% 5 g intravaginally at bedtime for 7 d	• Treat even if asymptomatic • Metronidazole 2 g PO single dose or 500 mg bid x 7 d (alternative) • Symptomatic pregnant women should be treated with 2 g metronidazole once
<b>Other</b>	• Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole • Routine treatment of partner(s) not recommended (not sexually transmitted)	• Associated with recurrent preterm labour, preterm birth and postpartum endometritis • Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action) • Routine treatment of partner(s) not recommended (not sexually transmitted)	• Warnings accompanying metronidazole use • Treat partner(s)

## Sexually Transmitted Infections (STIs)

- see [Family Medicine](#), FM46

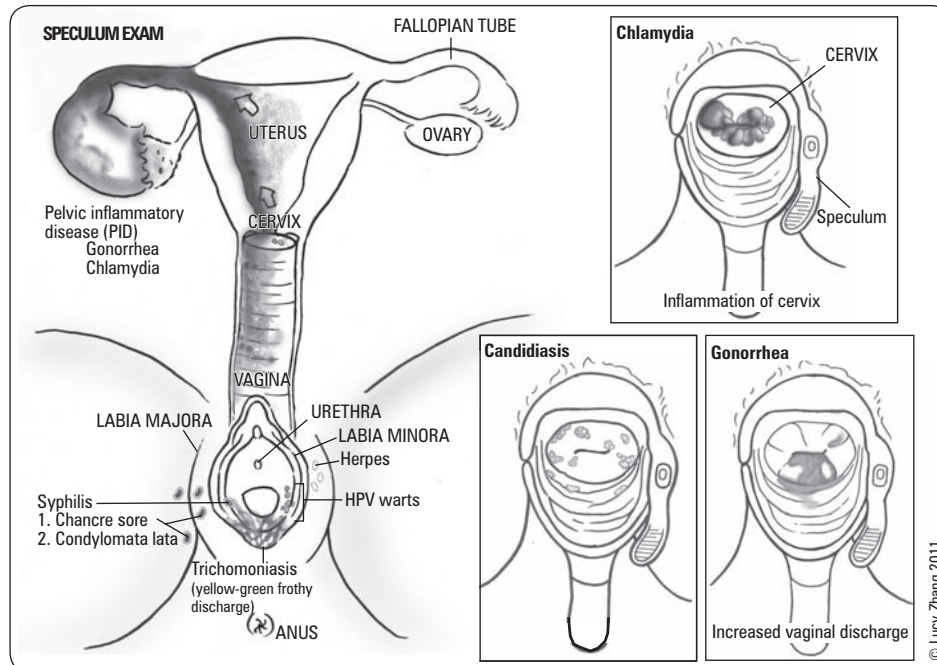


Figure 12. Speculum exam

### TRICHOMONIASIS

- see *Infectious Vulvovaginitis*, Table 14, GY25

### CHLAMYDIA

#### Etiology

- *Chlamydia trachomatis*

#### Epidemiology

- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae*

#### Clinical Features

- asymptomatic (80% of women)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- post-coital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

#### Investigations

- cervical culture or nucleic acid amplification test
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and vaginal tests now available, which are equally or more effective than cervical culture

#### Treatment

- doxycycline 100 mg PO bid for 7d or azithromycin 1 g PO in a single dose (may use in pregnancy)
- also treat gonorrhea because of high rate of co-infection
- treat partners
- reportable disease
- test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

#### Screening

- high risk groups
- during pregnancy
- with initiation of OCP (independent risk factor)



#### STI Testing

- Vaginal swab
  - Tests for bacterial vaginosis, trichomoniasis, candida
- Cervical swab
  - Tests for gonorrhea and chlamydia



#### Risk Factors for STIs

- History of previous STI
- Contact with infected person
- Sexually active individual < 25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Street involvement (homelessness, drug use)



#### Public Health Agency of Canada: National Reportable STIs

- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis

## Complications

- acute salpingitis, PID
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- infertility: tubal obstruction from low grade salpingitis
- ectopic pregnancy
- chronic pelvic pain
- perinatal infection: conjunctivitis, pneumonia

## GONORRHEA

### Etiology

- *Neisseria gonorrhoeae*
- symptoms and risk factors same as with chlamydia

### Investigations

- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal and throat culture (if clinically indicated)

### Treatment

- single dose of ceftriaxone 250 mg IM, or cefixime 800 mg PO
- if pregnant: above regimen or 2 g spectinomycin IM (avoid quinolones)
- also treat chlamydia, because of high rate of co-infection
- treat partners
- reportable disease
- screening as with Chlamydia

## HUMAN PAPILLOMAVIRUS (HPV)

### Etiology

- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

### Clinical Features

- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

### Investigations

- cytology (see *Cervical Screening Pap Test*, GY43)
  - koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

### Treatment

- patient administered:
  - podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  - imiquimod (Aldara®) 5% cream 3x/wk qhs x 16 wk
- provider administered:
  - cryotherapy with liquid nitrogen: repeat q1-2wk
  - podophyllin resin in tincture of benzoin: weekly
  - trichloroacetic acid (TCA) or bichloroacetic acid weekly (80-90%); safe in pregnancy
  - surgical removal/laser
  - intralesional interferon

### Prevention

- vaccination: Gardasil®, Cervarix® see Table 25, GY44
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)



Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated. Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant.



### Genital Warts During Pregnancy

- Condyloma tend to get larger in pregnancy and should be treated early (consider excision)
- C-section only if obstruction of birth canal or risk of extensive bleeding.
- Do not use imiquimod, podophyllin or podofilox



### Human Rights in Health Equity: Cervical Cancer and HPV Vaccines

*Am J Law Med* 2009;35:365-387

- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer
- In most developing countries cervical cancer rates have risen or remained unchanged
- Must recognize that cervical cancer disparities between race groups, urban and rural residence, and high and low SES are attributed to disparate screening and vaccination coverage
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited health care settings, sexual health stigma and related privacy concerns



## HERPES SIMPLEX VIRUS (HSV) OF VULVA

### Etiology

- 90% are HSV-2, 10% are HSV-1

### Clinical Features

- may be asymptomatic
- initial symptoms: present 2-21 d following contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent and shorter in duration (especially with HSV-1)

### Investigations

- viral culture preferred in patients with ulcer present, however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear)
  - multinucleated giant cells, acidophilic intranuclear inclusion bodies
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)
- HSV DNA PCR

### Treatment

- first episode
  - acyclovir 400 mg PO tid x 7-10 d, or famciclovir 250 mg PO tid x 7-10 d, or valacyclovir 1 g PO bid x 7-10 d
- recurrent episode
  - acyclovir 400 mg PO tid x 3-5 d, or famciclovir 125 mg PO bid x 3-5 d, or valacyclovir 500 mg PO bid x 3 d
- daily suppressive therapy
  - consider if 6-8 recurrences per year
  - acyclovir 400 mg PO bid, or famciclovir 250 mg bid, or valacyclovir 0.5-1 g PO OD
- severe disease
  - consider IV therapy acyclovir 5-10 mg/kg IV q8h x 5-7 d
- education regarding transmission
- avoid contact from onset of prodrome until lesions have cleared
- use barrier contraception



#### Classically

**HSV I:** disease above the belt (oral).

**HSV II:** disease below the belt (genital).



#### HSV Infections During Pregnancy

- Antiviral suppression of women with first episode or history of HSV infections from 36 wk GA on
- C-section should be performed on women who have active genital lesions at time of delivery
- Treatment: acyclovir 400 mg PO tid

## SYPHILIS

### Etiology

- *Treponema pallidum*

### Classifications

- primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based fleshy grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths or neonatal death



#### Epidemiology of Genital Ulcers

HSV	70-80%
1° syphilis	5%
Chancroid ( <i>haemophilus ducreyi</i> )	<1%

### Investigations

- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis)
  - spirochetes
- non-treponemal screening tests (VDRL, RPR); nonreactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

### Treatment

- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
  - treat partners, reportable disease
- treatment of latent syphilis >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
- screening
  - high risk groups
  - in pregnancy (see [Obstetrics](#), Table 13, OB21)

### Complications

- if untreated, 1/3 will experience late complications

### HIV

- see [Infectious Diseases](#), ID41



## Bartholinitis/Bartholin Gland Abscess

### Etiology

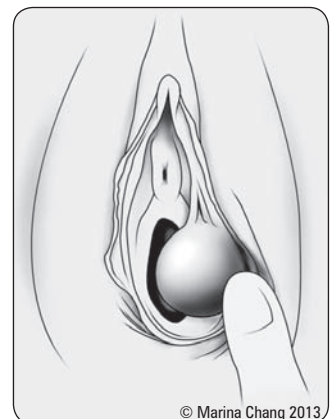
- often anaerobic and polymicrobial
- *U. urealyticum*, *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *P. mirabilis*, *Streptococcus* spp., *S. aureus* (rare)
- blockage of duct

### Clinical Features

- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

### Treatment

- sitz baths, warm compresses
- antibiotics: cephalexin x 1 wk
- incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
- marsupialization under general anesthetic – more definitive treatment
- rarely treated by removing gland



**Figure 13. Bartholin's gland abscess**

## Pelvic Inflammatory Disease (PID)

- up to 20% of all gynecology-related hospital admissions

### Etiology

- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
  - gonorrhea and chlamydia often co-exist
  - endogenous flora: anaerobic, aerobic, or both
    - ♦ *E. coli*, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Bacteroides*, *Peptostreptococcus*, *H. influenzae*, *G. vaginalis*
    - ♦ cause of recurrent PID
    - ♦ associated with instrumentation
  - *Actinomyces israelii* (Gram-positive, non acid-fast anaerobe)
    - ♦ 1-4% of PID cases associated with IUDs
  - others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

### Risk Factors

- age <30 yr
- risk factors as for chlamydia and gonorrhea
- vaginal douching
- IUD (within first 10 d after insertion)
- invasive gynecologic procedures (D&C, endometrial biopsy)



#### PID

Inflammation of the upper genital tract (above cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum, ± contiguous structures.



PID accounts for up to 20% of all gynecology hospital admissions.

### Clinical Presentation

- up to 2/3 asymptomatic: many subtle or mild symptoms
- common
  - fever  $>38.3^{\circ}\text{C}$
  - lower abdominal pain and tenderness
  - abnormal discharge: cervical or vaginal
- uncommon
  - nausea and vomiting
  - dysuria
  - AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

### Investigations

- bloodwork
  - $\beta$ -hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for *N. gonorrhoeae*, *C. trachomatis*
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

### Treatment

- must treat with polymicrobial coverage
- inpatient if:
  - moderate to severe illness
  - atypical infection
  - adnexal mass, tubo-ovarian or pelvic abscess
  - unable to tolerate oral antibiotics or failed oral therapy
  - immunocompromised
  - pregnant
  - adolescent – first episode
  - surgical emergency cannot be excluded (e.g. ovarian torsion)
  - PID is secondary to instrumentation
  - recommended treatment
    - ♦ cefoxitin 2 g IV q6h (no longer available in U.S.A.) or cefotetan 2 g IV q12h + doxycycline 100 mg IV/PO q12h or
    - ♦ clindamycin 900 mg IV q8h + gentamicin 2 mg/kg IV loading dose then gentamicin 1.5 mg/kg q8h maintenance dose
    - ♦ continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO bid to complete 14 d
    - ♦ percutaneous drainage of abscess under U/S guidance
    - ♦ when no response to treatment, laparoscopic drainage
    - ♦ if failure, treatment is surgical (salpingectomy, TAH/BSO)
- outpatient if:
  - typical findings
  - mild to moderate illness
  - oral antibiotics tolerated
  - compliance ensured
  - follow-up within 48-72 h (to ensure symptoms not worsening)
  - recommended treatment:
    - ♦ ofloxacin 400 mg PO bid x 14 d or levofloxacin 500 mg PO bid x 14 d  $\pm$  metronidazole 500 mg PO bid x 14 d (if suspect abscess)
    - ♦ ceftriaxone 250 mg IM x 1 + doxycycline 100 mg PO bid x 14 d or cefoxitin 2 g IM x 1 + probenecid 1 g PO + doxycycline 100 mg PO bid  $\pm$  metronidazole 500 mg PO bid x 14 d
    - ♦ consider removing IUD after a minimum of 24 h of treatment
    - ♦ reportable disease
    - ♦ treat partners
    - ♦ consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection



#### PID Complications

##### I FACE PID

Infertility  
 Fitz-Hugh-Curtis syndrome  
 Abscesses  
 Chronic pelvic pain  
 Ectopic pregnancy  
 Peritonitis  
 Intestinal obstruction  
 Disseminated infection (sepsis, endocarditis, arthritis, meningitis)



#### PID Diagnosis

- **Must** have:
  - Lower abdominal pain
- **Plus** one of:
  - Cervical motion tenderness
  - Adnexal tenderness
- **Plus** one or more of:
  - High risk partner
  - Temperature  $>38^{\circ}\text{C}$
  - Mucopurulent cervical discharge
  - Positive culture for *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, or other vaginal flora
  - Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
  - Leukocytosis
  - Elevated ESR or CRP (not commonly used)



Treat PID with **FOXY DOXY**  
 (cefoxitin + doxycycline)



#### Alternative PID Treatments

For patients with contraindications to treatment with cephalosporins or quinolones, recent evidence suggests that a short course of azithromycin at a dose of either 250 mg PO daily for 1 wk or 1 g PO weekly for 2 wk combined with metronidazole is effective in achieving a clinical cure for acute PID.

Source: Update to the Canadian Guidelines on Sexually Transmitted Infections. January 2010.

**Complications of Untreated PID**

- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID → 13% infertility
  - 2 episodes of PID → 36% infertility
- bacteremia
- septic arthritis, endocarditis

**Toxic Shock Syndrome**

- see [Infectious Diseases](#), ID26

**Risk Factors**

- tampon use
- diaphragm, cervical cap or sponge use (prolonged use, i.e. >24 h)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

**Clinical Presentation**

- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness

**Treatment**

- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics, e.g. cloxacillin
- steroid use controversial but if started within 72 h, may reduce severity of symptoms and duration of fever

**Toxic Shock Syndrome**

Multiple organ system failure due to *S. aureus* exotoxin (rare condition).

**Surgical Infections****Post-Operative Infections in Gynecological Surgery**

- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, discharge involving vaginal cuff
  - treat if fever and leukocytosis with broad spectrum antibiotics, i.e. clindamycin and gentamicin
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see [General Surgery](#), *Post-Operative Fever*, GS7

**Sexual Abuse**

- see [Family Medicine](#), FM28, [Emergency Medicine](#), ER29

**Sexuality and Sexual Dysfunction****SEXUAL RESPONSE**

1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

**SEXUAL DYSFUNCTION****Etiology**

- intrapsychic: patient's life experiences, value system
- relationship/interpersonal issues
- physical/organic

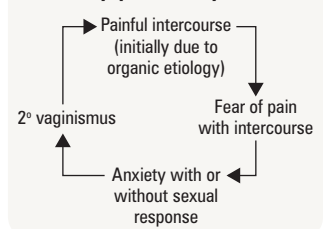
### Classification

- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but now unable to
- dyspareunia (3-6%): painful intercourse, superficial or deep
  - vaginismus (15%)
  - vulvodynia
  - vaginal atrophy
  - vulvar vestibulitis: associated with history of frequent yeast infections
  - PID

### Treatment

- lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
- dyspareunia
  - Kegel and reverse Kegel exercises
  - dilator treatment
  - comfort with self-exam
  - psychotherapy, other behavioural techniques
  - female on top position: allows for control of speed and duration
  - vestibulitis: remove local irritants, change in contraceptive methods, and dietary changes (increased citrate, decreased oxalate), vestibulectomy (rare)
  - vulvodynia: local moisturization, cold compresses, systemic nerve blocking therapy (amitriptyline, gabapentin), topical anesthetics, estrogen cream
  - pain clinic

#### Dyspareunia Cycle



#### Kegel Exercises

Regular contraction and relaxation to strengthen pelvic floor muscles.

#### Reverse Kegel Exercises

1 s contraction then 5 s of relaxation.



#### Menopause

Occurrence of last spontaneous menstrual period, resulting from loss of ovarian function (loss of oocyte response to gonadotropins).

#### "Being in menopause"

Lack of menses for 1 yr.

#### Perimenopause

Period of time surrounding menopause (2-8 yr preceding + 1 yr after last menses) characterized by fluctuating hormone levels, irregular menstrual cycles, and symptom onset.



- 85% of women experience hot flashes
- 20-30% seek medical attention
- 10% are unable to work



- Osteoporosis is the single most important health hazard associated with menopause
- Cardiovascular disease is the leading cause of death post-menopause



- Increased risk of breast cancer (RR 1.3) is associated with estrogen + progesterone HRT, but not with estrogen-only HRT
- All women taking HRT should have periodic surveillance and counseling regarding its benefits and risks

## Menopause

- see [Family Medicine](#), FM42

### Definitions

- lack of menses for 1 yr
- types of menopause
  - physiological; average age 51 yr (follicular atresia)
  - premature ovarian failure; before age 40 (autoimmune disorder, infection, Turner's syndrome)
  - iatrogenic (surgical/radiation/chemotherapy)

### Clinical Features

- associated with estrogen deficiency
  - vasomotor instability (tends to dissipate with time)
    - ♦ hot flashes/flushes, night sweats, sleep disturbances, formication, nausea, palpitations
  - urogenital atrophy involving vagina, urethra, bladder
    - ♦ dyspareunia, pruritus, vaginal dryness, bleeding, urinary frequency, urgency, incontinence
  - skeletal
    - ♦ osteoporosis, joint and muscle pain, back pain
  - skin and soft tissue
    - ♦ decreased breast size, skin thinning/loss of elasticity
  - psychological
    - ♦ mood disturbance, irritability, fatigue, decreased libido, memory loss

### Investigations

- increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH). But FSH level not always predictive due to monthly variation. Use absence of menses for 1 yr to diagnose
- decreased levels of estradiol (later)

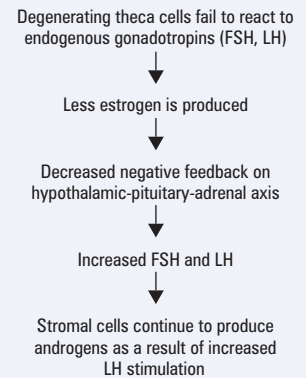
### Treatment

- goal is for individual symptom management
  - vasomotor instability
    - ♦ HRT (first line), SSRIs, venlafaxine, gabapentin, propranolol, clonidine
    - ♦ acupuncture
  - vaginal atrophy
    - ♦ local estrogen: cream (Premarin\*), vaginal suppository (VagiFem\*), ring (Estring\*)
    - ♦ lubricants (Replens\*)
  - urogenital health
    - ♦ lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery

- osteoporosis
  - 1000-1500 mg calcium OD, 800-1000 IU vitamin D, weight-bearing exercise, quit smoking
  - bisphosphonates (e.g. alendronate)
  - selective estrogen receptor modifiers (SERMs): raloxifene (Evista®) – mimics estrogen effects on bone, avoids estrogen-like action on breast and uterine cancer; does not help hot flashes
  - HRT: second-line treatment (unless for vasomotor instability as well)
- decreased libido
  - vaginal lubrication, counseling, androgen replacement (testosterone cream or the oral form Andriol®)
- cardiovascular disease
  - management of cardiovascular risk factors
- mood and memory
  - antidepressants (first line), HRT (augments effect)
- alternative choices (not evidence-based, safety not established)
  - black cohosh, phytoestrogens, St. John's wort, ginkgo biloba, valerian, evening primrose oil, ginseng, Don Quai



#### Menopause Pathophysiology



#### Absolute Contraindications to HRT

##### ABCD

Acute liver disease  
 Undiagnosed vaginal Bleeding  
 Cancer (breast/uterine), Cardiovascular disease  
 DVT (thromboembolic disease)

## Hormone Replacement Therapy (HRT)

- see [Family Medicine](#), FM42
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 yr)

### HRT Components

- estrogen
  - oral or transdermal (e.g. patch, gel)
  - transdermal preferred for women with hypertriglyceridemia or impaired hepatic function, smokers and women who suffer from headaches associated with oral HRT
  - low-dose (preferred dose: 0.3 mg Premarin®/25 µg Estradot® patch, can increase if necessary)
- progestin
  - given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

**Table 15. Examples of HRT Regimens**

HRT Regimen	Estrogen Dose	Progestin Dose	Notes
<b>Unopposed Estrogen</b>	CEE 0.625 mg PO OD	None	If no intact uterus
<b>Standard-dose</b>	CEE 0.625 mg PO OD	MPA 2.5 mg PO OD, or micronized progesterone 100 mg PO OD	Withdrawal bleeding may occur in a spotty, unpredictable manner Usually abates after 6-8 mo due to endometrial atrophy Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy)
<b>Standard-dose Cyclic</b>	CEE 0.625 mg PO OD	MPA 5-10 mg PO days 1-14 only, or micronized progesterone 200 mg PO OD days 1-14 only	Bleeding occurs monthly after day 14 of progestin (can continue for years) PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT
<b>Pulsatile</b>	CEE 0.625 mg PO OD	MPA low-dose	3 d on, 3 d off
<b>Transdermal</b>	Estroderm®-Estradiol 0.05 mg/d or 0.1 mg/d Estalis®-Estradiol 140 µg/d or 250 µg/d	Estroderm®-MPA 2.5 mg PO OD Estalis®-NEA 50 µg/d	Use patch twice weekly Can use oral progestins (Estroderm®) Combined patches available (Estalis®)

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate  
 Consider lower dose regimens, PREMPRO® 0.45/1.5 (Premarin® 0.45 mg and Provera® 1.5 mg)

### Side Effects of HRT

- abnormal uterine bleeding
- mastodynia – breast tenderness
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

### Contraindications to HRT

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease



- relative
  - pre-existing uncontrolled hypertension
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - diabetes mellitus (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

#### WOMEN'S HEALTH INITIATIVE (WHI) (launched in 1991)

- two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old
  - continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
  - estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy
- both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm
- the apparent increase in CHD was in disagreement with results of previous observational trial
- results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results
- benefits and risks reported as number of cases per 10,000 women each year

**Table 16. HRT Benefits versus Risks**

Benefits	Risks
<b>Vasomotor Symptoms:</b> less frequent and severe with use of either combined or estrogen-alone HRT	<b>Stroke:</b> 8 additional cases with combined HRT, and 12 additional cases for estrogen alone (WHI)
<b>Osteoporosis:</b> 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT. 6 fewer cases of hip fractures with estrogen alone	<b>DVT/PE:</b> 18 additional cases with combined HRT, and 9 additional cases for estrogen-alone (WHI)
<b>Colon Cancer:</b> 6 fewer cases with combined HRT (WHI). One additional case with estrogen-alone	<b>CHD:</b> 7 additional MIs with combined HRT (WHI). Secondary analysis suggests greater absolute risk for women aged > 70 yr and for women who start HRT > 10 yr post-menopause
	<b>Breast Cancer:</b> 8 additional cases with combined HRT (WHI). Risk only increased after > 5 yr of combined HRT use. No increased risk for estrogen-alone
	<b>Dementia and Mild Cognitive Impairment:</b> 50% greater risk of developing dementia in women taking estrogen-alone after age 65. Risk is greater for women taking combined HRT. Risk of developing dementia was reduced for women taking HRT before age 65



## Urogynecology



### Pelvic Relaxation/Prolapse

#### Etiology

- relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
- related to:
  - vaginal childbirth
  - aging
  - decreased estrogen (post-menopause)
  - following pelvic surgery
  - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  - congenital (rarely)
  - ethnicity (Caucasian women > Asian or African women)
  - collagen disorders

#### GENERAL CONSERVATIVE TREATMENT

- (for pelvic relaxation/prolapse and urinary incontinence)
- Kegel exercises
- local vaginal estrogen therapy
- vaginal pessary (intravaginal suspension disc)



#### Pelvic Relaxation/Prolapse

Protrusion of pelvic organs into or out of the vagina.

Table 17. Pelvic Prolapse

Type	Clinical Features	Treatment
<b>Uterine Prolapse</b> (protrusion of cervix and uterus into vagina)	<ul style="list-style-type: none"><li>Groin/back pain (stretching of uterosacral ligaments)</li><li>Feeling of heaviness/pressure in the pelvis<ul style="list-style-type: none"><li>Worse with standing, lifting</li><li>Worse at the end of the day</li><li>Relieved by lying down</li></ul></li><li>Ulceration/bleeding (particularly if hypoestrogenic)</li><li>± urinary incontinence</li></ul>	<ul style="list-style-type: none"><li>See <i>General Conservative Treatment</i>, GY34</li><li>Vaginal hysterectomy ± surgical prevention of vault prolapse</li><li>Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present</li></ul>
<b>Vault Prolapse</b> (protrusion of apex of vaginal vault into vagina, post-hysterectomy)		<ul style="list-style-type: none"><li>See <i>General Conservative Treatment</i>, GY34</li><li>Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension</li></ul>
<b>Cystocele</b> (protrusion of bladder into the anterior vaginal wall)	<ul style="list-style-type: none"><li>Frequency, urgency, nocturia</li><li>Stress incontinence</li><li>Incomplete bladder emptying ± associated increased incidence of urinary tract infections – may lead to renal impairment</li></ul>	<ul style="list-style-type: none"><li>See <i>General Conservative Treatment</i>, GY34</li><li>Anterior colporrhaphy (“anterior repair”)</li><li>Consider additional/alternative surgical procedure if documented urinary stress incontinence</li></ul>
<b>Rectocele</b> (protrusion of rectum into posterior vaginal wall)	<ul style="list-style-type: none"><li>Straining/digitation to evacuate stool</li><li>Constipation</li></ul>	<ul style="list-style-type: none"><li>See <i>General Conservative Treatment</i>, GY34</li><li>Also laxatives and stool softeners</li><li>Posterior colporrhaphy (“posterior repair”), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)</li></ul>
<b>Enterocele</b> (prolapse of small bowel in upper posterior vaginal wall)		<ul style="list-style-type: none"><li>Similar to hernia repair</li><li>Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated</li></ul>



**Grading of Pelvic Organ Prolapse**

- 0 = no descent during straining
- 1 = distal portion of prolapse > 1 cm above level of hymen
- 2 = distal portion of prolapse ≤ 1 cm above or below level of hymen
- 3 = distal portion of prolapse > 1 cm below level of hymen but without complete vaginal eversion
- 4 = complete eversion of total length of lower genital tract
- **Procidentia:** failure of genital supports and complete protrusion of uterus through the vagina



The only **true** hernia of the pelvis is an **ENTEROCELE** because peritoneum herniates with the small bowel.

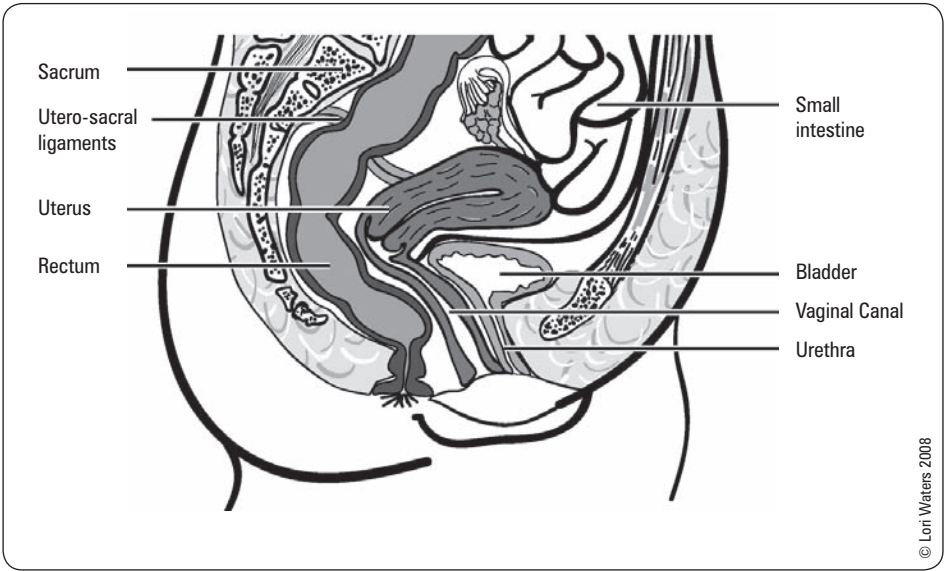
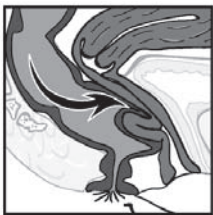


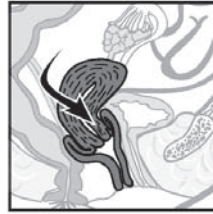
Figure 14. Pelvic anatomy



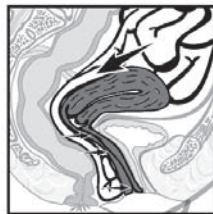
**Rectocele**



**Cystocele**



**Uterine Prolapse**



**Enterocele**

**Figure 15. Rectocele, cystocele, uterine prolapse, enterocele**

## Urinary Incontinence

- see [Urology](#), U6

### STRESS INCONTINENCE

#### Risk Factors for Stress Incontinence in Women

- pelvic prolapse
- pelvic surgery
- vaginal delivery
- hypoestrogenic state (post-menopause)
- age
- smoking
- neurological/pulmonary disease

#### Treatment

- see *General Conservative Treatment*, GY34
- surgical
  - tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

### URGE INCONTINENCE

#### Definition

- urine loss associated with an abrupt, sudden urge to void
- “overactive bladder”
- diagnosed based on symptoms

#### Etiology

- idiopathic (90%)
- detrusor muscle overactivity (“detrusor instability”)

#### Associated Symptoms

- frequency, urgency, nocturia, leakage

#### Treatment

- behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
- Kegel exercises
- medications
  - anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  - tricyclic antidepressants: imipramine



#### Stress Incontinence

Involuntary loss of urine with increased intra-abdominal pressure (coughing, laughing, sneezing, walking, running).



The gold standard diagnostic test for urinary incontinence is multichannel urodynamics. A large proportion of cases are correctly diagnosed from clinical history alone and this can be supplemented with patient urinary and intake diaries.

Systemic review and evaluation of methods of assessing urinary incontinence. *Health Technol Assess* 2006;10:1-132.



#### Urge Incontinence

Urine loss associated with an abrupt, sudden urge to void.



#### Rule Out Neurological Causes of Urge Incontinence

- Multiple sclerosis
- Herniated disc
- Diabetes mellitus



## Gynecological Oncology

### Uterus

### ENDOMETRIAL CARCINOMA

#### Epidemiology

- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5-yr survival for stage I disease
- 70-80% overall 5-yr survival for all stages

#### Risk Factors

- Type I: excess estrogen (estrogen unopposed by progesterone)
  - obesity
  - PCOS
  - unbalanced HRT (balanced HRT is protective)
  - nulliparity
  - late menopause
- estrogen-producing ovarian tumours (e.g. granulosa cell tumours)
- HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome
- tamoxifen



#### Incidence of Malignant Gynecological Lesions in North America

endometrium > ovary > cervix > vulva  
> vagina > fallopian tube



#### Complications of Therapy:

- Surgical site infection
- Lymphedema
- Radiation fibrosis
- Cystitis
- Proctitis

- Type II: not estrogen-related
  - possibly tamoxifen

### Classification and Clinical Features

- Type I (well-differentiated endometrioid adenocarcinoma) ~80% of cases:
  - postmenopausal bleeding in majority, abnormal uterine bleeding in majority of affected premenopausal women (menorrhagia, intermenstrual bleeding)
- Type II (serous, clear cell carcinoma, grade 3 endometrioid, undifferentiated, carcinosarcoma) ~15% of cases:
  - may not present with bleeding in early stage, more likely to present with advanced stage disease with symptoms like ovarian cancer (i.e. bloating, bowel dysfunction, pelvic pressure)

### Investigations

- endometrial sampling:
  - office endometrial biopsy
  - D&C ± hysteroscopy
- ± pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
  - not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

**Table 18. FIGO Staging of Endometrial Cancer (2009)**

Stage	Description	Stage	Description
I	<b>Confined to corpus</b>	IIIC	Metastasis to pelvic ± para-aortic LNs
IA	No or less than half myometrial invasion	IIIC1	Positive pelvic LN
IB	Invades through ≥½ of myometrium	IIIC2	Positive para-aortic LN ± positive pelvic LNs
II	<b>Tumour invades cervical stroma, but does not extend beyond uterus*</b>	IV	<b>Invasion of bladder ± bowel mucosa ± distant metastases</b>
		IVA	Invasion of bladder ± bowel mucosa
III	<b>Local and/or regional spread of the tumour</b>	IVB	Distant mets, including intra-abdominal mets ± inguinal LNs
IIIA	Invasion of serosa, corpus uteri ± adnexae		
IIIB	Vaginal ± parametrial involvement		

FIGO: International Federation of Gynecology and Obstetrics

\*Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

### Spread

- direct extension is most common
- lymphatic spread to pelvic and para-aortic nodes
- transtubal dissemination to peritoneal cavity
- hematogenous spread (usually to lungs, liver)

### Treatment

- surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
  - goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
  - laparoscopic approach associated with improved quality of life (optimal for most patients)
- adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
- chemotherapy: often used for recurrent disease (especially if high grade or aggressive histology)
- hormonal therapy: progestins can be used for recurrent disease (especially if low grade)

### UTERINE SARCOMA

- rare; 2-6% of all uterine malignancies
- arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
- behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5-yr survival is 35%
- vaginal bleeding is most common presenting symptom



#### Risk Factors for Endometrial Cancer

##### COLD NUT

Cancer (ovarian, breast, colon)

Obesity

Late menopause

Diabetes mellitus

Nulliparity

Unopposed estrogen: PCOS, anovulation, HRT

Tamoxifen: chronic use



Postmenopausal bleeding = endometrial cancer until proven otherwise.  
95% present with vaginal bleeding.



An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding.



#### True Pelvis

Area of pelvis between pelvic inlet and outlet, i.e. it does not include the abdominal contents in the pelvis found above the pelvic inlet.



#### Prognostic Factors

Most important is FIGO stage

Other Prognostic Factors:

- Age
- Grade
- Histologic subtype
- Depth of myometrial invasion
- Presence of lymphovascular space involvement (LVSI)
- Hormone receptor status



#### Uterine Sarcoma – Symptoms

##### BAD-P

Bleeding

Abdominal distention

Foul smelling vaginal Discharge

Pelvic Pressure

**Table 19. Summary of Uterine Sarcoma Subtypes and Features**

Type	Epidemiology	Features	Diagnosis	Treatment
<b>PURE TYPE</b>				
<b>1. Leiomyosarcoma</b>	<ul style="list-style-type: none"> <li>Accounts for 40%</li> <li>Average age of presentation is 55 yr but may present in pre-menopause</li> <li>Often coexists with benign leiomyomata (fibroids)</li> <li>50% arise within a fibroid ("sarcomatous degeneration")</li> </ul>	<ul style="list-style-type: none"> <li>Histologic distinction from leiomyoma               <ol style="list-style-type: none"> <li>Increased mitotic count (&gt;10 mitoses/10 high power fields)</li> <li>Tumour necrosis</li> <li>Cellular atypia</li> </ol> </li> <li>Rapidly enlarging fibroids in a pre-menopausal woman</li> <li>enlarging fibroids in a postmenopausal woman</li> </ul>	<ul style="list-style-type: none"> <li>Often postoperatively after uterus removed for presumed fibroids</li> <li>Staging using FIGO 2009 staging for Leiomyosarcomas</li> </ul>	<ul style="list-style-type: none"> <li>Hysterectomy/BSO usually</li> <li>No routine pelvic lymphadenectomy</li> <li>Adjuvant chemotherapy may be used if tumour has spread beyond uterus, for palliation</li> <li>Radiation therapy does not improve local control or survival</li> <li>Poor outcomes overall, even for early stage disease</li> </ul>
<b>2. Endometrial Stromal Sarcoma (ESS)</b>	<ul style="list-style-type: none"> <li>Accounts for 10-15%</li> <li>Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding</li> </ul>	<ul style="list-style-type: none"> <li>Abnormal uterine bleeding</li> <li>Good prognosis</li> </ul>	<ul style="list-style-type: none"> <li>Diagnosed by histology of endometrial biopsy or D&amp;C</li> <li>Staging using FIGO 2009 staging for ECC and Adenosarcoma</li> </ul>	<ul style="list-style-type: none"> <li>Hysterectomy/BSO (remove ovaries as ovarian hormones may stimulate growth)</li> <li>No routine pelvic lymphadenectomy</li> <li>Adjuvant therapy based on stage and histologic features (hormones and/or radiation)</li> <li>Hormonal therapy (progestins) may be used for metastatic disease</li> </ul>
<b>3. Undifferentiated Sarcoma</b>	<ul style="list-style-type: none"> <li>Accounts for 5-10%</li> </ul>	<ul style="list-style-type: none"> <li>Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis and lack smooth muscle or endometrial stromal differentiation</li> <li>Poor prognosis</li> </ul>	<ul style="list-style-type: none"> <li>Often found incidentally postoperatively for abnormal bleeding</li> </ul>	<ul style="list-style-type: none"> <li>Treatment primarily surgical</li> <li>Radiation and/or chemotherapy for advanced disease or unresectable disease</li> </ul>
<b>MIXED TYPE</b>				
<b>4. Adenosarcoma</b>	<ul style="list-style-type: none"> <li>The rarest of the uterine sarcoma</li> <li>Mixed tumour of low malignant potential</li> </ul>	<ul style="list-style-type: none"> <li>Present with abnormal vaginal bleeding</li> <li>Polypoid mass in uterine cavity</li> </ul>	<ul style="list-style-type: none"> <li>Mixture of benign epithelium with malignant low-grade sarcoma</li> <li>Often found incidentally at time of hysterectomy for PMB</li> </ul>	<ul style="list-style-type: none"> <li>Treatment is surgical with TAH/BSO</li> </ul>
<b>RECLASSIFIED</b>				
<b>5. Carcinosarcoma</b>	<ul style="list-style-type: none"> <li>Most common (43%)</li> <li>Recently reclassified as high grade endometrioid carcinoma with associated metaplasia of the mesenchyme, rather than arising separately from stroma</li> <li>Surgical staging using FIGO 2009 staging for endometrial cancer</li> </ul>	<ul style="list-style-type: none"> <li>Both epithelial and stromal malignant elements present</li> <li>Tend to form bulky polypoid masses that often fill uterine cavity and extend into or through the endocervical canal – often have extrauterine disease at presentation</li> </ul>	<ul style="list-style-type: none"> <li>Diagnosed by histology of endometrial biopsy or D&amp;C</li> </ul>	<ul style="list-style-type: none"> <li>Usually treated as "high grade endometrial carcinoma" since behaviour and treatment similar (i.e. surgical staging and resection of any gross metastatic disease, adjuvant chemotherapy and radiation)</li> </ul>

**Table 20. FIGO Staging of Uterine Sarcoma (2009)**

Stage	Description	Stage	Description
<b>I</b>	<b>Tumour limited to uterus</b>	<b>III</b>	
IA	<5 cm	IIIA	Tumour invades abdominal tissues, one site
IB	>5 cm	IIIB	Metastasis to pelvic and/or para-aortic lymph nodes
		IIIC	Tumour invades bladder and/or rectum
<b>II</b>	<b>Tumour extends beyond uterus</b>	<b>IV</b>	
IIA	To the pelvis, adnexal involvement	IVA	Tumour invades bladder and/or rectum
IIB	To extra-uterine pelvic tissue	IVB	Distant metastasis



A rapidly enlarging uterus, especially in a postmenopausal woman, should prompt consideration of leiomyosarcoma.

## Ovary



### BENIGN OVARIAN TUMOURS

- see Table 21
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour – rare



#### Ovarian Tumor Markers

- Epithelial cell – CA-125
- Stromal
  - Granulosa cell – inhibin
  - Sertoli-Leydig – androgens
- Germ cell
  - Dysgerminoma – LDH
  - Yolk sac – AFP
- Choriocarcinoma –  $\beta$ -hCG
- Immature Teratoma – none
- Embryonal cell – AFP +  $\beta$ -hCG



## MALIGNANT OVARIAN TUMOURS

- see Table 21

### Epidemiology

- lifetime risk 1.4% (1/70)
- in women >50 yr, more than 50% of ovarian tumours are malignant
- causes more deaths in North America than all other gynecologic malignancies combined
- 4th leading cause of cancer death in women
- 65% epithelial; 35% non-epithelial
- 5-10% of epithelial ovarian cancers are related to hereditary predisposition

### Risk Factors (for epithelial ovarian cancers)

- excess estrogen:
  - nulliparity
  - early menarche/late menopause
- age
- family history of breast, colon, endometrial, ovarian cancer
- race: Caucasian

### Protective Factors (for epithelial ovarian cancers)

- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
- pregnancy/breastfeeding
- tubal ligation (recently questioned)
- hysterectomy (without removal of ovaries)
- BSO (prophylactic surgery performed for this reason in high risk women – i.e. BRCA mutation carriers)

### Screening

- no effective method of mass screening
- routine CA-125 level measurements or U/S not recommended
  - high false positive rates
- controversial in high risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
  - familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
  - other cancers (e.g. endometrial, breast, colon)
  - BRCA-1 or BRCA-2 mutation: may recommend prophylactic bilateral oophorectomy after age 35 or when child-bearing is completed

### Clinical Features

- most women with epithelial ovarian cancer present with advanced stage disease since often “asymptomatic” until disseminated disease (symptoms with early stage disease are vague and non-specific)
- when present, symptoms may include:
  - abdominal symptoms (nausea, bloating, dyspepsia, anorexia, early satiety)
  - symptoms of mass effect
    - ♦ increased abdominal girth – from ascites or tumour itself
    - ♦ urinary frequency
    - ♦ constipation
  - postmenopausal bleeding; irregular menses if pre-menopausal (rare)

### Low Malignant Potential (also called “Borderline”) Tumours

- pregnancy, OCP and breastfeeding are protective factors
- ~15% of all epithelial ovarian tumours
- tumour cells display malignant characteristics histologically, but no invasion is identified
- able to metastasize, but not commonly
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
  - NO proven benefit of chemotherapy
- generally slow growing, excellent prognosis
  - 5-yr survival >99%
  - recurrences tend to occur late, may be associated with low grade serous carcinoma



#### Ovaries are like GEMS

Germ-cell  
Epithelial  
Metastatic  
Sex cord stromal



#### Risk/Protective Factors for Epithelial Ovarian Cancer

##### NO CHILD

Nulliparity  
OCP, breast-feeding, tubal ligation, hysterectomy (protective)  
Caucasian  
Family History  
Increasing age (>40)  
Late menopause  
Delayed child-bearing



**Effects of screening on ovarian cancer mortality: The prostate, lung, colorectal and ovarian cancer screening randomized controlled trial**  
JAMA 2011;305:2295-2303

**Objective:** To evaluate the effect of screening for ovarian cancer with CA-125 and transvaginal ultrasound on mortality in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial.

**Participants:** 78,216 women aged 55-74 yr.

**Study Groups:** Intervention group – annual screening with CA-125 for 6 yr, transvaginal ultrasound for 4 yr; control group – no CA-125 or transvaginal ultrasound screening, received usual medical care.

**Follow-up:** Maximum 13 yr (median, 12.4 yr).

**Outcome Measures:** Mortality from ovarian cancer, including primary fallopian tube cancers. Secondary outcomes included ovarian cancer incidence and complications associated with screening, examinations and diagnostic procedures.

**Results:** Of those diagnosed with ovarian cancer in the intervention and usual care group, the mortality was 3.1% and 2.6% respectively. 15% of women undergoing diagnostic evaluation following a false positive screening test suffered a complication of the procedure.

**Conclusions:** Simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false positive screening test was associated with complications.



Any adnexal mass in postmenopausal women should be considered malignant until proven otherwise.



Most (70%) epithelial ovarian cancers present at stage III disease.



Diagnosis of ovarian tumours requires surgical pathology.



Table 21. Ovarian Tumours




Type	Description	Presentation	Ultrasound/Cytology	Treatment
<b>FUNCTIONAL TUMOURS (all benign)</b>				
<b>Follicular cyst</b> 	Follicle fails to rupture during ovulation	Usually asymptomatic May rupture, bleed, tort, infarct causing pain $\pm$ signs of peritoneal irritation	4-8 cm mass, unilocular, lined with granulosa cells	Symptomatic or suspicious masses warrant surgical exploration Otherwise if < 6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle OCP (ovarian suppression) – will prevent development of new cysts Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)
<b>Lutein cyst</b>	Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic	More likely to cause pain than follicular cyst May delay onset of next period	Larger (10-15 cm) and firmer than follicular cysts	Same as for follicular cysts
<b>Theca-lutein cyst</b>	Due to atretic follicles stimulated by abnormal $\beta$ -hCG levels	Associated with molar pregnancy, ovulation induction with clomiphene		Conservative Cyst will regress as $\beta$ -hCG levels fall
<b>Luteoma of pregnancy</b>	Usually bilateral Due to prolonged elevation of $\beta$ -hCG	Associated with multiple pregnancy		Same as for theca-lutein (conservative) Regresses postpartum
<b>Endometrioma</b>	See <i>Endometriosis</i> , GY16			
<b>Polycystic Ovaries</b>				
<b>BENIGN GERM-CELL TUMOURS</b>				
<b>Benign cystic teratoma (dermoid)</b> 	Single most common ovarian germ cell neoplasm Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)	May rupture, twist, infarct 20% bilateral 20% occur outside of reproductive yr	Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic	Treatment usually laparoscopic cystectomy; may recur
<b>MALIGNANT GERM-CELL TUMOURS</b>				
<b>General Information</b>	Rapidly growing, 2-3% of all ovarian cancers	Usually children and young women (<30 yr)		Surgical resection (often conservative unilateral salpingo-oophorectomy $\pm$ nodes) $\pm$ chemo
<b>Dysgerminoma</b>	Produces lactate dehydrogenase (LDH)	10% bilateral		Usually very responsive to chemotherapy, therefore complete resection is not necessary for cure
<b>Immature teratoma</b>	No tumour marker identified			
<b>Yolk sac tumour</b>	Produces fetoprotein (AFP) Rare	Unilateral		More aggressive subtype, often need chemo (bleomycin, etoposide, cisplatin, BEP)
<b>Embryonal</b>	Produces AFP and $\beta$ -hCG			
<b>Carcinoma</b>	Rare			
<b>Choriocarcinoma</b>	Produces $\beta$ -hCG			
<b>Mixed Germ Cell</b>	Depends on type of tumour involved			
<b>EPITHELIAL OVARIAN TUMOURS (malignant or borderline)</b>				
<b>General Information</b>	Derived from mesothelial cells lining peritoneal cavity Classified based on histologic type 80-85% of all ovarian neoplasms (includes malignant)		Varies depending on subtype	<b>Borderline</b> Cystectomy vs. unilateral salpingo-oophorectomy <b>Malignant</b> 1. Early stage (stage 1): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy) 2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatin/paclitaxel versus Intraperitoneal chemotherapy (stage III) Neoadjuvant chemotherapy with IV carboplatin/paclitaxel followed by delayed debulking with further adjuvant IV chemotherapy
<b>Serous</b>	Most common ovarian tumour 50% of all ovarian cancers 75% of epithelial tumours 70% benign	20-30% bilateral	Lining similar to fallopian tube epithelium Often multilocular Histologically contain Psammoma bodies (calcified concentric concretions)	

Table 21. Ovarian Tumours (continued)

Type	Description	Presentation	Ultrasound/Cytology	Treatment
<b>EPITHELIAL OVARIAN TUMOURS (malignant or borderline)</b>				
<b>Mucinous</b>	20% of epithelial tumours 85% benign	Rarely complicated by <i>Pseudomyxoma peritonei</i> : implants seed abdominal cavity and produce large quantities of mucin	Resembles endocervical epithelium Often multilocular May reach enormous size	Poor response to chemotherapy If mucinous, remove appendix as well to rule out possible source of primary disease
<b>Endometrioid</b>	20% of epithelial ovarian Ca High malignant potential		Histology resembles endometrium	
<b>Clear cell</b>	≤1% of epithelial ovarian Ca High malignant potential		Histology resembles mesonephric cells	
<b>Brenner tumour</b>	≤1% of epithelial ovarian Ca Majority benign		Fibrotic tumour with transitional cell-like epithelial core	
<b>SEX CORD STROMAL OVARIAN TUMOURS</b>				
<b>General Information</b>				Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease
<b>Fibroma/thecoma (benign)</b>	From mature fibroblasts in ovarian stroma	Non-functioning Occasionally associated with Meig's syndrome (benign ovarian tumour and ascites and pleural effusion)	Firm, smooth rounded tumour with interlacing fibrocytes	
<b>Granulosa-theca cell tumours (benign or malignant)</b>	Can be associated with endometrial cancer Inhibin is tumour marker	Estrogen-producing → feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding)	Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies	
<b>Sertoli-Leydig cell tumour (benign or malignant)</b>	Can measure elevated androgens as tumour markers	Androgen-producing → virilizing effects (hirsutism, deep voice, recession of front hairline)		
<b>METASTATIC OVARIAN TUMOURS</b>				
<b>From GI tract, breast, endometrium, lymphoma</b>	4-8% of ovarian malignancies Krukenberg tumour – metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast) with "signet-ring" cells			

### Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
    - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynaecologic oncology referral (see sidebar)
- bloodwork: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
- radiology:
  - bone scan or PET scan not indicated
  - transvaginal ultrasound best to visualize ovaries
  - CT scan abdomen and pelvis to look for metastatic disease
- try to rule out other primary source if suspected, based on:
  - occult blood per rectum: endoscopy ± barium enema
  - gastric symptoms, gastroscopy ± upper GI series
  - abnormal vaginal bleeding, endometrial biopsy to rule out concurrent endometrial cancer, colposcopy ± ECC to rule out cervical cancer if abnormal cervix
  - breast lesion identified or risk factors present: mammogram



**A Risk of Malignancy Incorporating CA125, Ultrasound and Menopausal Status for the Accurate Preoperative Diagnosis of Ovarian Cancer**  
BJOG 1990;97:922-929

$RMI = U \times M \times CA-125$

Ultrasound Findings (1 pt for each)

- Multilocular cyst
  - Evidence of solid areas
  - Evidence of metastases
  - Presence of ascites
  - Bilateral lesions
- $U = 1$  (for U/S scores of 0 or 1)  
 $U = 4$  (for U/S scores of 2-5)

Menopausal Status

- Postmenopausal:  $M = 4$
- Pre-menopausal:  $M = 1$

Absolute Value of CA-125 Serum Level  
 • For  $RMI > 200$ : Gynecologic oncology referral is recommended

**Table 22. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2009)**

Stage	Description
<b>I</b>	<b>Growth limited to the ovaries</b>
IA	1 ovary, no ascites, no tumour on external surface, capsule intact
IB	2 ovaries, no ascites, no tumour on external surface, capsule intact
IC	1 or 2 ovaries with any of the following: capsule ruptured, tumour on ovarian surface or malignant cells in ascites
<b>II</b>	<b>Growth involving one or both ovaries with pelvic extension</b>
IIA	Extension ± metastases to uterus/tubes
IIB	Extension to other pelvic structures
IIC	II A/B with malignant cells in ascites or positive peritoneal washings
<b>III</b>	<b>Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver mets is Stage III</b>
IIIA	Microscopic peritoneal metastasis beyond pelvis, LNs negative
IIIB	Macroscopic peritoneal metastasis beyond pelvis <2 cm, LNs negative
IIIC	Implant >2 cm and/or retroperitoneal or inguinal nodes
<b>IV</b>	<b>Distant metastasis beyond peritoneal cavity</b>

FIGO: International Federation of Gynecology and Obstetrics

**Causes of Elevated CA-125**

- Age influences reliability of test as a tumour marker
- 50% sensitivity in early stage ovarian cancer (poor) – therefore not good for screening

**Malignant**

- Gyn: ovary, uterus
- Non-Gyn: pancreas, stomach, colon, rectum

**Non Malignant**

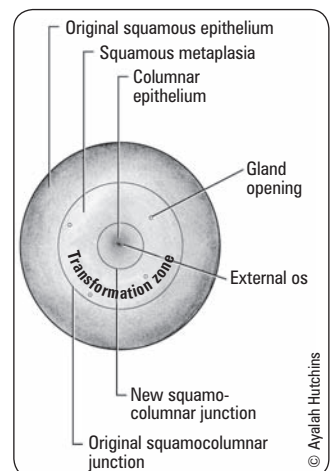
- Gyn: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyn: cirrhosis, pancreatitis, renal failure



CA-125 is indicated for monitoring response to treatment.

**Malignant Ovarian Tumour Prognosis**

<b>5-yr Survival</b>	
Stage I	75-95%
Stage II	60-75%
Stage III	23-41%
Stage IV	11%

**Figure 16. The cervix**

## Cervix

**BENIGN CERVICAL LESIONS**

- Nabothian cyst/inclusion cyst
  - no treatment required
- endocervical polyps
  - treatment is polypectomy (office procedure)

**MALIGNANT CERVICAL LESIONS****Epidemiology**

- majority are squamous cell carcinomas (95%); adenocarcinomas increasing (5%); rare subtypes include small cell, adenosquamous
- 8,000 deaths annually in North America
- annual Pap test reduces a woman's chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

**Etiology**

- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from squamous to columnar)
  - a new squamocolumnar junction forms as a result
- the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
- dysplasia → carcinoma in situ (CIS) → invasion
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

**Risk Factors**

- HPV infection
  - see *Sexually Transmitted Infections*, GY27
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
- high risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high risk male partner
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include:
  - immigrant Canadians
  - First Nations Canadians
  - geographically isolated Canadians
  - sex-trade workers
  - low socioeconomic status

Cervical Cancer Screening Guidelines (Pap Test)

- see [Family Medicine](#), FM4

Clinical Features

- squamous cell carcinoma (SCC): exophytic, fungating tumour
- adenocarcinoma: endophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - post-coital bleeding
- late
  - 80-90% present with bleeding: either post-coital, postmenopausal or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened or ulcerated area visible on cervix



Cervical cancer is caused by HPV infection.

Table 23. Cytological Classification: Terminology Used to Describe Lesions

Bethesda Grading System (Pap Test Cytology)	Classic System/Cervical Intraepithelial Neoplasia (CIN) Grading System (Biopsy)
Within normal limits	Normal
Infection	Inflammatory atypia (organism)
Reactive and reparative changes	
Squamous cell abnormalities	
Atypical squamous cells of undetermined significance (ASCUS)	Squamous atypia of uncertain significance
Atypical squamous cells, cannot exclude HSIL (ASC-H)	
Low grade squamous intraepithelial lesion (LSIL)	HPV atypia or mild dysplasia (CIN I)
High grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia (CIN II) Severe dysplasia (CIN III) Carcinoma in situ (CIS)
Squamous cell carcinoma (SCC)	Squamous cell carcinoma (SCC)
Glandular cell abnormalities	
Atypical glandular cells of undetermined significance (AGUS)	Glandular atypia of uncertain significance
Endocervical adenocarcinoma	Adenocarcinoma
Endometrial adenocarcinoma	
Extrauterine adenocarcinoma	
Adenocarcinoma, not otherwise specified (NOS)	



**The Bethesda Classification System** is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. The diagnosis of cervical intraepithelial neoplasia (CIN) or cervical carcinoma requires a tissue sample, obtained by biopsy of suspicious lesions (done during colposcopy), to make a histologic diagnosis.

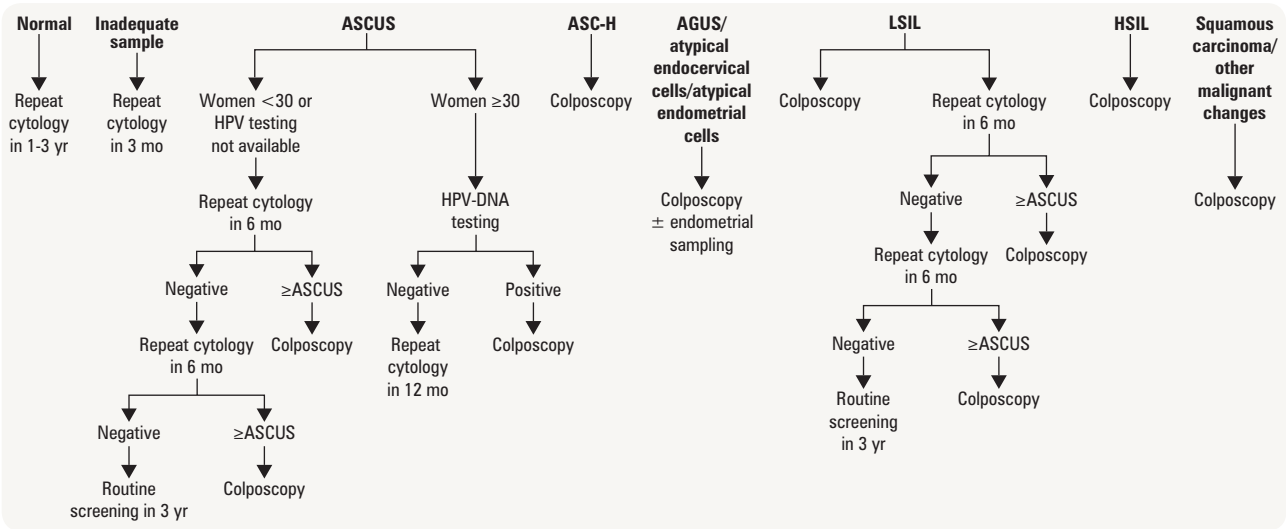


Figure 17. Decision making chart for Pap test (not applicable for adolescents)

Adapted from Ontario Cervical Screening Practice Guidelines. May 2012. Cervical screening guidelines unique to each province.

## Diagnosis

- see *Colposcopy*, GY9
- apply acetic acid and identify acetowhite lesions, punctation, mosaicism, and abnormal blood vessels to guide cervical biopsy
- endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
- diagnostic excision (loop electrosurgical excision procedure, LEEP) if:
  - lesion extends into endocervical canal
  - positive ECC
  - discrepancy between Pap test results and colposcopy
  - microinvasive carcinoma
- consider cold knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including EUA), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, IVP, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

**Table 24. FIGO Staging Classification of Cervical Cancer (Clinical Staging)**

Stage	Description
<b>I</b>	<b>Confined to cervix</b>
IA	Microinvasive (diagnosed only by microscopy)
IA <sub>1</sub>	Stromal invasion not >3 mm deep, not >7 mm wide
IA <sub>2</sub>	3-5 mm deep; not >7 mm wide
IB	Clinically visible lesion confined to cervix, or microscopic lesion >IA
IB <sub>1</sub>	Clinically visible lesion ≤4 mm in greatest dimension
IB <sub>2</sub>	Clinically visible lesion >4 mm in greatest dimension
<b>II</b>	<b>Beyond uterus but not to the pelvic wall or lower 1/3 of vagina</b>
IIA	No obvious parametrial involvement
IIA <sub>1</sub>	Clinically visible lesion ≤4 mm in greatest dimension
IIA <sub>2</sub>	Clinically visible lesion >4 mm in greatest dimension
IIB	Obvious parametrial involvement
<b>III</b>	<b>Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney</b>
IIIA	Involves lower 1/3 vagina but no extension into pelvic side wall
IIIB	Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney
<b>IV</b>	<b>Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum</b>
IVA	Spread of the growth to adjacent organs
IVB	Distant metastases

## Treatment: Prevention and Management

### Prevention: HPV Vaccine

- two vaccines currently approved (Gardasil®, Cervarix®)

**Table 25. Comparison of Two Vaccines against Human Papillomavirus (HPV)**

	Gardasil®	Cervarix®
Viral strains covered	6, 11, 16, 18	16, 18
Route of administration	IM	IM
Schedule of dosing	0, 2, 6 mo	0, 1, 6 mo
Side effects	Local: redness, pain, swelling General: headache, low grade fever, GI upset	Local: redness, pain, swelling General: headache, low grade fever, GI upset
Approved age	Females age 9-45, males age 9-26	Females age 10-25
Contraindications	Pregnant women and women who are nursing (limited data)	

- for optimal benefit of vaccination, should be administered before onset of sexual activity (i.e. before exposure to virus)
- may be given at the same time as Hep B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 d after last dose of vaccination



### Liquid-based Cytologic Smear Study and Conventional Papanicolaou Smears: A Meta-analysis of Prospective Studies Comparing Cytologic Diagnosis and Sample Adequacy

*Am J Obstet Gynecol* 2001;185:308-317

**Purpose:** To assess the cytologic diagnosis and sample adequacy of liquid-based cervical cytologic smear (ThinPrep) versus conventional Papanicolaou smear.

**Study:** Systematic review of prospective trials comparing ThinPrep and conventional Pap smears. Main outcomes: Frequency of diagnoses of ASCUS, LSIL, HSIL; and adequacy of sample collection (i.e. contains squamous cells, endocervical cells, and possibly metaplastic cells).

**Results:** 25 studies met the selection criteria (n=533,039 women; 221,864 in ThinPrep group; 378,659 in conventional smear group; 67,484 in both groups). Liquid-based smears (ThinPrep) had significantly improved cytologic diagnosis of LSIL (OR = 1.27 to 2.15) and diagnosis of HSIL (OR = 2.26), but no difference in rate of diagnosis of ASCUS (OR = 1.03). Liquid-based Pap smear also resulted in improved sample adequacy (OR = 1.64 to 2.11).

**Conclusion:** Liquid-based cytologic smears resulted in better diagnosis of cervical premalignant lesions (HSIL and LSIL) and improved sample adequacy, compared to conventional Pap smears.



### Prophylactic Vaccination Against Human Papillomavirus Infection in Women: A Systematic Review of Randomized Controlled Trials

*CMAJ* 2007;177:469-479

**Purpose:** To assess the effectiveness of HPV vaccination for preventing HPV infection and precancerous cervical lesions.

**Study:** Systematic review of studies of prophylactic HPV vaccination.

**Data Sources:** MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials, and the Cochrane Library.

**Patients:** Of 457 studies, nine were included in the review (six of these were RCTs). A total of 40,323 females were enrolled. All participants had received HPV vaccinations that included coverage of the HPV 16 strain.

**Main outcomes:** Frequency of high-grade cervical lesions, persistent HPV infection, low-grade cervical lesions, external genital lesions, adverse events, and death.

**Results:** HPV vaccination was associated with a reduction in the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared with control groups. The HPV vaccination was also found to be efficacious in reducing persistent HPV infection, low-grade lesions, and genital warts.

**Conclusion:** Prophylactic vaccination of women between 15-25 yr not previously infected with vaccine-type HPV strains, has been found to be efficacious in preventing HPV infection and precancerous cervical lesions.

**Table 26. Management of Patients Abnormal Cervical Histology and Cervical Cancer**

Management	
CIN I	<ul style="list-style-type: none"> <li>Preferred option for biopsy-proven CIN I is observation</li> <li>Repeat assessment and cytology in 12 mo</li> <li>Management according to cytology results</li> </ul> If after HSIL or AGC <ul style="list-style-type: none"> <li>Cytology and histology should be reviewed</li> <li>If discrepancy remains, excisional biopsy may be considered</li> </ul>
CIN II and CIN III	Women over 25 yr <ul style="list-style-type: none"> <li>CIN II or III should be treated</li> <li>Excisional procedures preferred for CIN III</li> <li>Those with + margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage</li> <li>Treatment for recurrent CIN II or III should be by excision</li> </ul> Women less than 25 yr <ul style="list-style-type: none"> <li>Pathologist should be asked to clarify whether lesion is CIN II or CIN III</li> <li>CIN II: observe with colposcopy at 6-mo intervals for up to 24 mo before treatment considered</li> <li>CIN III: should be treated</li> </ul> During pregnancy: <ul style="list-style-type: none"> <li>CIN II or III suspected or diagnosed during pregnancy, repeat colposcopy and treatment delayed until 8-12 wk after delivery</li> </ul>
Stage IA <sub>1</sub> (no LVSI)	<ul style="list-style-type: none"> <li>Trachelectomy (removal of only the cervix) if future fertility desired (and lesion ≤2 cm)</li> <li>Simple hysterectomy if future fertility is not desired</li> </ul>
Stage IA <sub>2</sub> , IB <sub>1</sub>	<ul style="list-style-type: none"> <li>Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study)</li> <li>Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy</li> <li>Advantage is that ovaries can be spared if pre-menopausal</li> <li>For fertility preservation, may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease</li> <li>Concurrent chemoradiation therapy if adverse high risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria and/or positive margins</li> </ul>
Stages IB <sub>2</sub> (>4 cm), II, III, IV	<ul style="list-style-type: none"> <li>Primary chemoradiation therapy</li> <li>PET/CT to grade: evaluate pelvic and para-aortic nodes</li> <li>For positive nodes on PET: primary chemoradiation with extended field RT</li> <li>Hysterectomy generally not suggested following primary treatment with curative intent</li> </ul>

**Abnormal Pap Tests in Pregnancy**

- incidence: 1/2,200
- Pap test at all initial prenatal visits
  - if abnormal Pap or suspicious lesion, refer to colposcopy
- if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
- if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
- if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
  - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility) or concurrent chemoradiation therapy
  - recommendations in T2/T3: delay of therapy until viable fetus and C/S for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy



Cervical cancer is most prevalent in developing countries and therefore is the only gynecologic cancer that uses clinical staging. This facilitates consistent international staging with countries that do not have technologies such as CT and MRI.

**Cervical Cancer Prognosis****5-yr Survival**

Stage 0	99%
Stage I	75%
Stage II	55%
Stage III	30%
Stage IV	7%
Overall	50-60%

**PHAC National Advisory Committee on Immunization (NACI) Recommends Quadrivalent HPV4 Vaccine for Males**

- HPV4 (Gardasil®) is recommended in males between 9 and 26 yr of age for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2, and 3, anal cancer, and anogenital warts
- HPV4 (Gardasil®) is recommended in males between 9 and 26 yr of age (NACI Recommendation Grade B) for the prevention of penile, perianal and perineal intraepithelial neoplasias and associated cancers
- HPV4 (Gardasil®) is recommended in males who have sex with males (MSM) ≥9 yr of age
- Cervarix™ is not recommended in males at this time

Source: PHAC National Advisory Committee on Immunization (NACI). Update on human papillomavirus (HPV) vaccines. Canada Communicable Dis Rep 2012;38:ACS-1



## Vulva

**BENIGN VULVAR LESIONS****Non-Neoplastic Disorders of Vulvar Epithelium**

- biopsy is necessary to make diagnosis and/or rule out malignancy
- hyperplastic dystrophy (squamous cell hyperplasia)
  - surface thickened and hyperkeratotic
  - pruritus most common symptom
  - typically postmenopausal women
  - treatment: 1% fluorinated corticosteroid ointment bid for 6 wk
- lichen sclerosis
  - subepithelial fat becomes diminished, labia become thin and atrophic, membrane-like epithelium, labial fusion
  - pruritus, dyspareunia, burning
  - figure of 8' distribution
  - most common in postmenopausal women but can occur at any age
  - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down



Any suspicious lesion of the vulva should be biopsied.



- mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
  - hyperkeratotic areas with areas of thin, shiny epithelium
  - treatment: fluorinated corticosteroid ointment

### Tumours

- papillary hidradenoma, nevus, fibroma, hemangioma

## MALIGNANT VULVAR LESIONS

### Epidemiology

- 5% of genital tract malignancies
- 90% squamous cell carcinoma; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
  - Type I disease: HPV-related (50-70%)
    - ♦ more likely in younger women
    - ♦ 90% of vulvar intraepithelial neoplasia (VIN) contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    - ♦ usually postmenopausal women

### Risk Factors

- HPV infection (see above)
- VIN (vulvar intraepithelial neoplasia): precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  - progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)

### Clinical Features

- many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus or lesion most common
- less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal → pelvic nodes)
  - hematogenous

### Investigations

- ± colposcopy
- ALWAYS biopsy any suspicious lesion

**Table 27. FIGO Staging Classification and Treatment of Vulvar Cancer (Surgical Staging)**

Stage	Description	Treatment
0	<b>Intraepithelial neoplasia (VIN), carcinoma in situ</b>	Local excision/superficial vulvectomy Laser ablation Local immunotherapy (imiquimod)
I	<b>Tumour confined to vulva</b>	Radical local excision + groin node dissection if > 1 mm invasion
IA	≤2 cm lesion, confined to vulva, perineum ± stromal invasion ≤1 mm, no LN involvement	Sentinel node dissection acceptable if lesion < 4 cm and no suspicious nodes on examination
IB	>2 mm lesion or stromal invasion > 1 mm, confined to vulva or perineum, no LNs	
II	<b>Tumour any size with adjacent extension (1/3 lower urethra, 1/3 lower vagina or anus) with negative LN</b>	Individualized Radical surgical excision ± chemoradiation Neoadjuvant chemoradiation followed by surgical resection Assessment of regional nodes
III	<b>Tumour any size with or without extension to perineal structures plus positive inguino-femoral LNs</b>	Individualized Primary resection versus neoadjuvant chemoradiation followed by surgical resection
IIIA	LN met (≥5 mm) or 1-2 LN mets (<5 mm)	Chemoradiation ± radical surgical excision
IIIB	2 or more LN mets (≥5 mm) or >3 LNs mets (<5 mm)	
IIIC	Positive LNs with extracapsular spread	
IV	<b>Regional Invasion (2/3 upper urethra, 2/3 upper vagina or distal structures)</b>	Individualized Palliative therapy
	<b>Tumour invades any of the following:</b>	Individualized
IVA	1. Spread to upper urethra ± vaginal mucosa, bladder, rectal mucosa or fixed to pelvic bone	Chemoradiation ± radical surgical excision
IVB	2. Fixed or ulcerated inguino-femoral LN Distant mets including pelvic LN	

### Prognosis

- depends on stage – particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%

## Vagina

### BENIGN VAGINAL LESIONS

- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct, seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

### MALIGNANT VAGINAL LESIONS

#### Epidemiology

- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are squamous cell carcinoma
- more than 50% diagnosed between 70-90 yr old

#### Risk Factors

- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

#### Investigations

- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy!)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are actually metastatic from one of these sites)
- staging (see Table 29)

#### Clinical Features

**Table 28. Clinical Features of Malignant Vaginal Lesions**

Type	Clinical Features
<b>Vaginal Intra-Epithelial Neoplasia (VAIN)</b>	Grades: analogous to cervical dysplasia
<b>Squamous Cell Carcinoma (SCC)</b>	Most common site is upper 1/3 of posterior wall of vagina Asymptomatic Painless discharge and bleeding Vaginal discharge (often foul-smelling) Vaginal bleeding especially during/post-coitus Urinary and/or rectal symptom 2° to compression
<b>Adenocarcinoma</b>	Most are metastatic, usually from cervix, endometrium, ovary or colon Most primaries are clear cell adenocarcinomas 2 types: non-DES and DES syndrome

### Diethylstilbestrol (DES) Syndrome

- fetal exposure to DES (due to maternal use) predisposes to cervical or vaginal clear cell carcinoma: occurs in 30-95% of exposed females
- if exposed, <1 in 1,000 risk of developing clear cell adenocarcinoma
- clinical features
  - adenosis is persistent Müllerian type glandular epithelium in vagina
  - malformations of upper vagina, cervix, and interior of uterus (T-shaped); cockscomb or hooded cervix, cervical collar and pseudopolyps of cervix
- patients with DES exposure should have annual Pap tests (cervix and vagina) and digital vaginal exam for subepithelial masses
  - if any abnormality, refer for colposcopy

**Table 29. FIGO Staging Classification of Vaginal Cancer (Clinical Staging) and Treatment**

Stage	Description	Treatment
0	Intraepithelial neoplasia (VAIN), carcinoma in situ	<ul style="list-style-type: none"> <li>Must rule out invasive cancer via biopsies and colposcopy prior to conservative treatment</li> <li>Laser ablation vs. surgical excision vs. local immunotherapy (e.g. imiquimod)</li> </ul>
I	Limited to the vaginal wall	<ul style="list-style-type: none"> <li>Radiation is main stay of therapy: combination of brachytherapy and external beam radiation</li> <li>In certain situations where surgery has a role in management: <ol style="list-style-type: none"> <li>Stage I disease involving upper posterior vagina</li> <li>Young patients who require radiation therapy</li> <li>Stage IVA disease, particularly if rectovaginal or vesicovaginal fistula is present</li> <li>In patients with a central recurrence after radiation therapy</li> </ol> </li> <li>Limited reported evidence with chemoradiation</li> </ul>
II	Involves subvaginal tissue, NO pelvic wall extension	
III	Pelvic wall extension	
IV	Extension beyond true pelvis OR bladder/rectum involvement	
IVA	Bladder $\pm$ rectal mucosal spread $\pm$ extension beyond true pelvis	
IVB	Spread to distant organs	



**Prognosis**  
**5-yr Survival Rates**  
 Stage I 70%  
 Stage II 40%  
 Stage III 30%  
 Stage IV 15-20%

## Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)
- usually serous epithelial carcinoma
- recently considered to be origin of serous ovarian cancer
- more common in fifth and sixth decade

### Clinical Features

- classic triad present in minority of cases, but very specific
  - watery discharge (most specific) = "hydrops tubae profluens"
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain
- most patients present with a pelvic mass (see *Ovarian Cancer*, GY39 for guidelines regarding diagnosis/investigation)

### Treatment

- as for malignant epithelial ovarian tumours



**Classic Triad (<15% of patients)**

- Watery vaginal discharge
- Pelvic pain
- Vaginal bleeding



Current hypotheses suggest epithelial serous ovarian cancer originates from malignant fallopian tube cells.

## Gestational Trophoblastic Disease/Neoplasia (GTD/GTN)

- refers to a spectrum of proliferative abnormalities of the trophoblast

### Epidemiology

- 1/1000 pregnancies
- marked geographic variation – as high as 1/125 in Taiwan
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%



With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease!

### HYDATIDIFORM MOLE (Benign GTD)

#### Complete Mole

- most common type of hydatidiform mole
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues or membranes present
- 46XX or 46XY, chromosomes completely of paternal origin (90%)
- 2 sperm fertilize empty egg or 1 sperm with reduplication
- 15-20% risk of progression to malignant sequelae
- risk factors
  - geographic (South East Asia most common)
  - others (maternal age >40 yr,  $\beta$ -carotene deficiency, vitamin A deficiency) – not proven
- clinical features
  - often present during apparent pregnancy with abnormal symptoms/findings:
    - vaginal bleeding (97%)
    - excessive uterine size for LMP (51%)
    - theca-lutein cysts >6 cm (50%)
    - preeclampsia (27%)
    - hyperemesis gravidarum (26%)
    - hyperthyroidism (7%)
    - $\beta$ -hCG >100,000 IU/L
    - no fetal heart beat detected

### Partial (or Incomplete) Mole

- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXY, XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
- low risk of progression to malignant sequelae (<4%)
- associated with fetus, which may be growth-restricted and/or have multiple congenital malformations
- clinical features
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

### Investigations

- quantitative  $\beta$ -hCG levels (tumour marker) abnormally high for gestational age
- U/S findings:
  - if complete: no fetus (classic “snow storm” due to swelling of villi)
  - if partial: molar degeneration of placenta  $\pm$  fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - $\beta$ -hCG >100,000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts

### Treatment

- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- consider hysterectomy (if patient no longer desires fertility)
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

### Follow-up

- contraception required to avoid pregnancy during entire follow-up period
- serial  $\beta$ -hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of  $\beta$ -hCG indicates GTN  $\rightarrow$  patient needs chemotherapy

### GTN (MALIGNANT GTD)

#### Invasive Mole or Persistent GTN

- diagnosis made by rising or plateau in  $\beta$ -hCG, development of metastases following treatment of documented molar pregnancy (see sidebar)
- histology: molar tissue from D&C
- metastases are rare (4%)

#### Choriocarcinoma

- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

#### Placental-site Trophoblastic Tumour

- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low  $\beta$ -hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

### CLASSIFICATION of GTN

- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of  $\beta$ -hCG
  - negative metastases on staging investigations
- metastatic
  - 4% patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - ♦ lungs (80%): cough, hemoptysis, CXR lesion(s)
    - ♦ vagina (30%): vaginal bleeding, “blue lesions” on speculum exam
    - ♦ pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - ♦ liver (10%): elevated LFTs, U/S or CT findings
    - ♦ brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings



#### GTN Diagnosis

- $\beta$ -hCG plateau: <10% drop in  $\beta$ -hCG over four values in 3 wk (e.g. days 1, 7, 14 and 21) OR
- $\beta$ -hCG rise >20% in any two values over two wk or longer (e.g. measure at days 1, 7, 14) OR
- $\beta$ -hCG persistently elevated >6 mo OR
- Metastases on work-up



Lungs are #1 site for malignant GTN metastases. When pelvic exam and chest x-ray are negative, metastases are uncommon.

- highly vascular tumour → bleeding → anemia
- all have rising or plateau of  $\beta$ -hCG
- classification of metastatic GTN
  - ♦ divided into good prognosis and bad prognosis
  - ♦ features of bad prognosis
    - long duration (>4 mo from antecedent pregnancy)
    - high pre-treatment  $\beta$ -hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood
    - brain or liver metastases
    - prior chemotherapy
    - metastatic disease following term pregnancy
  - ♦ good prognosis characterized by the absence of each of these features

### Investigations – For Staging

- bloodwork: CBC, electrolytes, creatinine,  $\beta$ -hCG, TSH, LFTs
- imaging: CXR, U/S pelvis, CT abdo/pelvis, CT brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF  $\beta$ -hCG
  - ratio of plasma  $\beta$ -hCG:CSF  $\beta$ -hCG <60 indicates metastases

**Table 30. FIGO Staging and Management of Malignant GTN**

Stage	Findings	Management
I	Disease confined to uterine corpus	Single agent chemotherapy for low risk disease (WHO score $\leq 6$ ) 1st line: pulsed – actinomycin D (Act-D) IV q2wk Alternatives: MTX-based regimen 20% of patients need to switch to alternate single-agent regimen due to failure of $\beta$ -hCG to return to normal Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score $\geq 7$ ) or if resistant to single agent chemotherapy Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour
II	Metastatic disease to genital structures	As above
III	Metastatic disease to lungs with or without genital tract involvement	As above
IV	Distant metastatic sites including brain, liver, kidney, GI tract	Usually high risk (EMA-CO) with surgical resection of sites of disease Persistence/resistance to chemotherapy Consider radiation for brain mets

**Table 31. WHO Prognostic Score for GTD (2011)**

Prognostic Factor	Score			
	0	1	2	4
Maternal age	>40	40		
AP	Mole	Abortion	Term	
Interval (end of AP to chemotherapy in months)	<4	4-6	7-13	>13
HCG IU/l	<103	103-104	104-105	>105
Number of metastases	0	1-4	5-8	>8
Site of metastases	Lung	Spleen, kidney	GI tract	Brain, liver
Largest tumour mass		3-5 cm	>5 cm	
Prior chemotherapy			Single drug	Two drug

### Follow-up (for GTN)

- contraception for all stages to avoid pregnancy during entire follow-up period
- stage I, II, III
  - weekly  $\beta$ -hCG until 3 consecutive normal results
  - then monthly x 12 mo
- stage IV
  - weekly  $\beta$ -hCG until 3 consecutive normal results
  - then monthly x 24 mo

## Common Medications

Table 32. Common Medications

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
acyclovir (Zovirax®)	Antiviral; inhibits DNA synthesis and viral replication	<b>First Episode:</b> 400 mg PO tid x 7-10 d <b>Recurrence:</b> 400 mg PO tid x 5 d	Genital herpes	<b>S/E:</b> headache, GI upset <b>D/I:</b> zidovudine, probenecid
bromocriptine (Parlodel®)	Dopaminomimetic Agonist at D <sub>2</sub> R Antagonist at D <sub>1</sub> R Acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin	<b>Initial:</b> 1.25-2.5 mg PO qhs with food <b>Then:</b> increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response <b>Usual Range:</b> 1.5-15 mg OD <b>For IVF:</b> <b>Initial:</b> 1.25 mg/d PO between days 4-6 of follicular phase <b>Then:</b> 2.5 mg/d until 3 d after onset menstruation	Galactorrhea + amenorrhea 2° to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas) IVF	<b>S/E:</b> nausea, vomiting, headache, postural hypotension, somnolence <b>C/I:</b> uncontrolled hypertension, pregnancy-induced hypertension, CAD, breastfeeding <b>D/I:</b> domperidone, macrolides, octreotide
clomiphene citrate (Clomid®)	Increases output of pituitary gonadotropins which induces ovulation	50 mg OD x 5 d Try 100 mg or 160 mg OD if ineffective 3 courses = adequate trial	Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy	<b>S/E:</b> Common – hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare – ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects <b>C/I:</b> pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding
clotrimazole (Canesten®)	Antifungal; disrupt fungal cell membrane	<b>Tablet:</b> 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose <b>Cream</b> (1 or 2%): 1 applicator intravaginally qhs x 3-7 d <b>Topical:</b> apply bid x 7 d	Vulvovaginal candidiasis	<b>S/E:</b> vulvar/vaginal burning
danazol (Cyclomen® – CAN) (Danocrine® – US)	Synthetic steroid that inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties	200-800 mg in 2-3 divided doses Used for 3-6 mo Biannual hepatic U/S required if >6 mo use	Endometriosis 1° menorrhagia/DUB	<b>S/E:</b> weight gain, acne, mild hirsutism, hepatic dysfunction <b>C/I:</b> pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia, thromboembolic disease <b>D/I:</b> warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives
doxycycline	Tetracycline derivative; inhibit protein synthesis	100 mg PO bid x ≥7 d	Chlamydia, gonococcal infection, syphilis	<b>S/E:</b> GI upset, hepatotoxicity <b>C/I:</b> pregnancy, severe hepatic dysfunction <b>D/I:</b> warfarin, digoxin
fluconazole (Diflucan®)	Antifungal; disrupt fungal cell membrane	150 mg PO x 1 dose	Vulvovaginal candidiasis unresponsive to clotrimazole	<b>S/E:</b> headache, rash, nausea, vomiting, abdominal pain, diarrhea <b>D/I:</b> terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin
leuprolide (Lupron®)	Synthetic GnRH analog Induces reversible hypoestrogenic state	3.75 mg IM q1mo or 11.25 mg IM q3mo Usually ≤6 mo, check bone density if >6 mo Retreatment with Lupron® alone not recommended because of effects on bone density	Endometriosis Leiomyomata DUB Precocious puberty	<b>S/E:</b> hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset <b>C/I:</b> pregnancy, undiagnosed vaginal bleeding, breastfeeding
menotropin (Pergonal®)	Human Gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development	75-150 U of FSH and LH IM OD x 7-12 d, then 10,000 U hCG one day after last dose	Infertility	<b>S/E:</b> bloating, irritation at injection site, abdominal/pelvic pain, headache, nausea and vomiting, multiple pregnancy <b>C/I:</b> primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding
metronidazole (Flagyl®)	Bactericidal; forms toxic metabolites which damage bacterial DNA	2 g PO x 1 dose or 500 mg PO bid x 7 d	Bacterial vaginosis, trichomonas vaginitis	<b>S/E:</b> headache, dizziness, nausea, vomiting, diarrhea, disulfiram-like reaction (flushing, tachycardia, nausea and vomiting) <b>C/I:</b> pregnancy (1 <sup>st</sup> trimester) <b>D/I:</b> cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine



**Table 32. Common Medications** (continued)

Drug Name (Brand Name)	Action	Dosing Schedule	Indications	Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)
oxybutinin (Ditropan®)	Anticholinergic – relaxes bladder smooth muscle, inhibits involuntary detrusor contraction	5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d	Overactive bladder (urge incontinence)	<b>S/E:</b> dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache <b>C/I:</b> glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function
tolterodine (Detrol®)	Anticholinergic	1-2 mg PO bid	Overactive bladder (urge incontinence)	<b>S/E:</b> anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain <b>C/I:</b> glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function
tranexamic acid (Cyklokapron®)	Anti-fibrinolytic, reversibly inhibits plasminogen activation	1-1.5 g tid-qid for first 4 d of cycle Max 4 g/d Ophthalmic check if used for several wk	Menorrhagia	<b>S/E:</b> nausea, vomiting, diarrhea, dizziness, rare cases of thrombosis, abdominal pain, MSK pain <b>C/I:</b> thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age < 15 yr
urofollitropin (Metrodin®)	FSH	75 U/d SC x 7-12d	Ovulation induction in PCOS	<b>S/E:</b> ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy <b>C/I:</b> primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding
combined oral contraceptive pill (OCP)	Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration		Contraception Disorders of menstruation	See Tables 8-12
intrauterine device (IUD) copper IUD (Nova-T®) progesterone-releasing IUD (Mirena®)	<b>Copper IUD:</b> mild foreign body reaction in endometrium which is toxic to sperm and alters sperm motility <b>Progesterone-releasing IUD:</b> decidualization of endometrium and thickening of cervical mucus, may suppress ovulation	Contraceptive effects last 5 yr	Same as above	See Table 8-12

## References

### Books/Manuals

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed, text revision. Washington: American Psychiatric Publishing, 2000.  
Berek JS, Hacker NF. Gynecologic oncology. 5th ed. Lippincott Williams & Wilkins, 2010.  
Dickey R. Managing contraceptive pill patients, 9th ed. EMIS Inc: Medical Publishers, 1998.  
Cunningham FG, McDonald PC, Gant NF. Williams obstetrics, 14th ed. Appleton and Lange, 1993.  
Hacker NF and Moore JG. Essentials of obstetrics and gynecology, 2nd ed. WB Saunders, 1992.

### Guidelines

ACOG Practice Bulletin – Clinical Management Guidelines for Obstetrician-Gynecologists. Premenstrual Syndrome. 2000;15.  
ARHP Quick Reference Guide for Clinicians. Managing premenstrual symptoms. June 2008.  
Bentley J, et al. SOGC Joint Clinical Practice Guidelines. Colposcopic management of abnormal cervical cytology and histology, 2012. JOGC 2012;284:1188-1202.  
Centers for Disease Control and Prevention (CDC). Recommendations on the use of quadrivalent human papillomavirus vaccine in males – Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep 2011;60:1705-1708.  
Davis V, Dunn S. Emergency postcoital contraception. SOGC Clinical Practice Guidelines July 2000;82.  
Guilbert E, Boroditsky R, Black A, Kives S, Leboeuf M, Mirosch M, Senikas V, Wagner MS, Weir E, York-Lowry J, Reid R, Trussell J. Society of Obstetricians and Gynaecologists of Canada. Canadian consensus guideline on continuous and extended hormonal contraception. J Obstet Gyn Canada 2007;29:S1-S32.  
National guideline for the treatment of bacterial vaginosis. Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). Sex Transm Infect 1999;75:S1 6-8.  
Ontario Cervical Screening Practice Guidelines. June 2005. Available from: <http://www.cancercare.on.ca/index> – cervical screening.htm.  
Paley PJ. Screening for the major malignancies affecting women: current guidelines. Am J Obstet Gynecol 2001;184:1021-1030.  
Public Health Agency of Canada, 2010. Canadian guidelines on sexually transmitted infections. (Updated January 2010.) Available from: <http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-lcdcits/index-eng.php>.  
Public Health Agency of Canada, 2011. Public health information update on the treatment of gonococcal infection. Available from: <http://www.phac-aspc.gc.ca/std-mts/sti-its/alert/2011/alert-gono-eng.php>.  
PHAC National Advisory Committee on Immunization (NACI). Update on human papillomavirus (HPV) vaccines. Canada Communicable Disease Report 2012;38:ACS-1.  
Reid R. Oral contraceptives and the risk of venous thromboembolism: an update. SOGC Clinical Practice Guideline. J Obstet Gyn Canada 2010;32:1192-1197.  
SOGC News Release. New recommendations from national ob/gyn society address Depo-Provera, bone loss. May 2006. Available from: [http://www.sogc.org/media/pdf/advisories/dmpa-may2006\\_e.pdf](http://www.sogc.org/media/pdf/advisories/dmpa-may2006_e.pdf).  
SOGC Clinical Practice Guidelines: Emergency Contraception. JOGC. Sep 2012;34(9):870-878. Available from: [http://www.sogc.org/guidelines/documents/gui280CPG1209E\\_000.pdf](http://www.sogc.org/guidelines/documents/gui280CPG1209E_000.pdf)  
SOGC Committee Opinion on Missed Hormonal Contraceptives: New recommendations. JOGC 2008;30:1050-1062. Available from: <http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf>.

### Journal Articles

Anderson, GL, Limacher, M, et al. (WHI Steering Committee). Effects of conjugated equine estrogen in postmenopausal women with hysterectomy – the women's health initiative randomized controlled trial. JAMA 2004;291:1701-1712.  
Bélisle S, Blake J, Basson R, et al. Canadian consensus conference on menopause, 2006 update. J Obstet Gynaecol Can 2006;28(2 Suppl 1):S1-S94.  
Berstein SJ, Sanchez-Ramos L, Ndujisi B. Liquid-based cervical cytologic smear study and conventional Papanicolaou smears: A metaanalysis of prospective studies comparing cytologic diagnosis and sample adequacy. Am J Obstet Gynecol 2001;185:308-317.  
Canadian Consensus Conference on Menopause, 2006 Update. JOGC 2006;171.

- Buys, SS, et al. Effect of screening on ovarian cancer mortality: the prostate, lung, colorectal and ovarian (PLCO) cancer screening randomized control trial. *JAMA* 2011;305:2295-2303.
- Creanga AA, Bradley HM, McCormick C, et al. Use of metformin in polycystic ovary syndrome: a meta-analysis. *Obstet Gynecol* 2008;111:959-968.
- Davey E, Barratt A, Irwig L et al. Effect of study design and quality of unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. *Lancet* 2006;367:122-132.
- Donnez J, Tomaszewski J, Vasquez F et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids *NEJM* 2012;366(5):421-432. doi:10.1056/NEJMoa1103180.
- Erdman JN. Human Rights in Health Equity: Cervical cancer and Hpv vaccines. *Am J Law & Medicine* 2009;35:365-387.
- Espeland, MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women – Women's health initiative memory study. *JAMA* 2004;291:2959-2968.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998;280:605-613.
- Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *BJOG* 1990;97:922-929.
- Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 2011;342:d2151. doi:10.1136/bmj.d2151.
- Klipping C, Duijkers I, Trummer D, et al. Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen. *Contraception* 2008;78:16-25.
- Lipscomb GH, McCord ML, Stovall TG, et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *NEJM* 2001;341:1974-1978.
- Luciano AA, Solima RG. Ectopic Pregnancy: From Surgical Emergency to Medical Management. *Ann NY Acad Sci* 2001;943:235-254.
- Manson JE, Martin KA. Postmenopausal hormone replacement therapy. *NEJM* 2001;345:34-40.
- Lujan ME, Chizen DR, Pierson RA. Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. *J Obstet Gyn Canada* 2008.
- Marchbanks PA, Aneger JF, Coulman CB, et al. Risk factors for ectopic pregnancy: a population based study. *JAMA* 1998;259:1823-1827.
- Martin JL, Williams KS, Abrams KR, et al. Systematic review and evaluation of methods of assessing urinary incontinence. *Health Technol Assess* 2006;10:1-132,iii-iv.
- MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane DB Syst Rev* 2004;18.
- Mantha S, Karp R, Raghavan V et al. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. *BMJ* 2012; 345:e4944.
- Ouellet-Hellstram R, Graham DJ, Staffa JA, Sidney S, et al. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. CHC-CVD final report 111022v2.
- Rambout L, Hopkins L, Fung Kee Fung M, et al. Prophylactic vaccination against human papillomavirus infection in women: a systematic review of randomized controlled trials. *CMAJ* 2007;177.
- Ratner S and Ofri D. Menopause and hormone replacement therapy. *West J Med* 2001;175:32-34.
- Rimsza ME. Counselling the adolescent about contraception. *Pediatr Rev* 2003;24:162-170.
- Rossouw JE, Prentice RL, Manson JE et al. Postmenopausal hormone therapy and risks of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465-1477.
- Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007;110:587-593.
- Shapter AP. Gestational trophoblastic disease. *Obs Gynecol Clin North Am* 2001;28:805-817.
- Shumaker SA, Legault C, Kuller L, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women – Women's Health Initiative Memory Study. *JAMA* 2004; 291:2947-2958.
- Tingulstad S, Hagen B, Skjeldestad FE, et al. The risk of malignancy index to evaluate potential ovarian cancers in local hospitals. *BR J Obstet Gynecol* 1999;93:448-452.
- Wooltorton, E. The Evra (ethinyl estradiol/norelgestromin) Contraceptive patch: estrogen exposure concerns. *CMAJ* 2006;174:164-165.
- Wooltorton E. Medroxyprogesterone acetate (Depo-Provera) and bone mineral density loss. *JAMA* 2005;172:746.
- Women's Health Coordinating Council. Clinician Information Sheet: HPV Vaccine for Cervical Cancer Prevention. Massachusetts General Hospital. August 21, 2006.

## Websites

- Management of Uterine Fibroids. Summary, Evidence Report/Technology Assessment: Number 34. AHRQ Publication No. 01-E051, January 2001.
- Agency for Healthcare Research and Quality, Rockville, MD. Available from: <http://www.ahrq.gov/clinic/utsumm.htm>.
- Sexuality and U. Society of Obstetricians and Gynaecologists of Canada. Available from: <http://www.sexualityanduc.ca>.

Lawson Eng and Anthony La Delfa, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

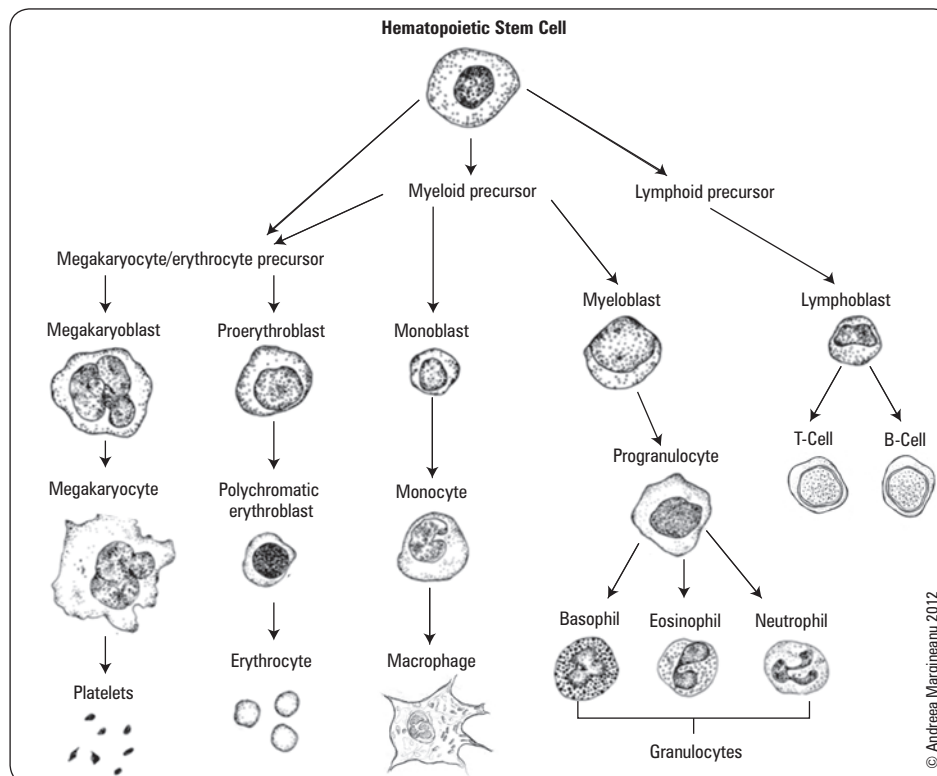
Dr. Martina Trinkaus and Dr. Richard Ward, staff editors

<b>Acronyms</b> .....	<b>2</b>	<b>Disorders of Secondary Hemostasis</b> .....	<b>29</b>
<b>Basics of Hematology</b> .....	<b>2</b>	Hemophilia A (Factor VIII Deficiency)	
Complete Blood Count (CBC)		Hemophilia B (Factor IX Deficiency)	
Blood Film Interpretation		Factor XI Deficiency	
Bone Marrow Aspiration and Biopsy		Liver Disease	
		Vitamin K Deficiency	
<b>Common Presenting Problems</b> .....	<b>5</b>	Disseminated Intravascular Coagulation (DIC)	
Anemia		<b>Venous Thromboembolism</b> .....	<b>31</b>
Erythrocytosis		Approach to Treatment of Venous	
Thrombocytopenia		Thromboembolism	
Thrombocytosis		<b>Hypercoagulable Disorders</b> .....	<b>34</b>
Pancytopenia		<b>Hematologic Malignancies and</b>	
Neutrophilia		<b>Related Disorders</b> .....	<b>35</b>
Neutropenia		<b>Myeloid Malignancies</b> .....	<b>35</b>
Lymphocytosis		Acute Myeloid Leukemia (AML)	
Lymphopenia		Myelodysplastic Syndromes (MDS)	
Eosinophilia		<b>Myeloproliferative Neoplasms (MPNs)</b> .....	<b>37</b>
Agranulocytosis		Chronic Myeloid Leukemia (CML)	
Leukemoid Reactions		Polycythemia Vera (PV)	
<b>Approach to Lymphadenopathy</b> .....	<b>11</b>	Idiopathic Myelofibrosis (IMF)	
<b>Approach to Splenomegaly</b> .....	<b>12</b>	Essential Thrombocythemia (ET)	
<b>Microcytic Anemia</b> .....	<b>12</b>	<b>Lymphoid Malignancies</b> .....	<b>41</b>
Iron Metabolism		Acute Lymphoblastic Leukemia (ALL)	
Iron Deficiency Anemia		<b>Lymphomas</b> .....	<b>42</b>
Anemia of Chronic Disease		Hodgkin Lymphoma	
Sideroblastic Anemia		Non-Hodgkin Lymphoma (NHL)	
Lead Poisoning		<b>Malignant Clonal Proliferations of</b>	
Thalassemia		<b>Mature B-Cells</b> .....	<b>46</b>
<b>Normocytic Anemia</b> .....	<b>16</b>	Chronic Lymphocytic Leukemia (CLL)	
Aplastic Anemia		Multiple Myeloma (MM)	
<b>Hemolytic Anemia (HA)</b> .....	<b>17</b>	Monoclonal Gammopathy of Unknown	
Thalassemia		Significance (MGUS)	
β-Thalassemia Minor (Thalassemia Trait)		Lymphoplasmacytic Lymphoma	
β-Thalassemia Major		(Waldenstrom's Macroglobulinemia)	
α-Thalassemia		<b>Complications of Hematologic Malignancies</b> ..	<b>49</b>
Sickle Cell Disease		Hyperviscosity Syndrome	
Autoimmune Hemolytic Anemia (AIHA)		Tumour Lysis Syndrome	
Microangiopathic Hemolytic Anemia (MAHA)		<b>Blood Products and Transfusions</b> .....	<b>50</b>
Hereditary Spherocytosis		Blood Products	
Hereditary Elliptocytosis		Red Blood Cells	
G6PD Deficiency		Platelets	
<b>Macrocytic Anemia</b> .....	<b>22</b>	Coagulation Factors	
Vitamin B <sub>12</sub> Deficiency		Acute Blood Transfusion Reactions	
Folate Deficiency		Delayed Blood Transfusion Reactions	
<b>Hemostasis</b> .....	<b>24</b>	<b>Common Medications</b> .....	<b>54</b>
Three Phases of Hemostasis		Antiplatelet Therapy	
<b>Disorders of Primary Hemostasis</b> .....	<b>25</b>	Anticoagulant Therapy	
Immune Thrombocytopenic Purpura (ITP)		Chemotherapeutic and Biological Agents used	
Heparin-Induced Thrombocytopenia (HIT)		in Oncology	
Thrombotic Thrombocytopenic Purpura (TTP)		<b>Landmark Hematology Trials</b> .....	<b>57</b>
and Hemolytic Uremic Syndrome (HUS)		<b>References</b> .....	<b>58</b>
Von Willebrand Disease (vWD)			

## Acronyms

AFIB	atrial fibrillation	HUS	hemolytic uremic syndrome	RAEB	refractory anemia with excess blasts
AIHA	autoimmune hemolytic anemia	IMF	idiopathic myelofibrosis	RARS	refractory anemia with ringed sideroblasts
ALL	acute lymphoblastic leukemia	IPC	intermittent pneumatic compression	RBC	red blood cells
AML	acute myeloid leukemia	IPSS	international prognostic scoring system	RCMD	refractory cytopenia with multilineage dysplasia
ANC	absolute neutrophil count	ITP	immune thrombocytopenic purpura	RCMD-RS	refractory cytopenia with multilineage dysplasia and ringed sideroblasts
APC	activated protein C	LMWH	low molecular weight heparin	RDW	RBC distribution width
APCR	activated protein C resistance	MAHA	microangiopathic hemolytic anemia	SPEP	serum protein electrophoresis
APS	antiphospholipid antibody syndrome	MCH	mean corpuscular Hb	sTfR	soluble transferrin receptor
CLL	chronic lymphocytic leukemia	MCHC	mean corpuscular Hb concentration	TIBC	total iron binding capacity
CML	chronic myeloid leukemia	MCV	mean corpuscular volume	TPO	thrombopoietin
DIC	disseminated intravascular coagulation	MDS	myelodysplastic syndromes	TTP	thrombotic thrombocytopenic purpura
EPO	erythropoietin	MGUS	monoclonal gammopathy of unknown significance	UFH	unfractionated heparin
ET	essential thrombocythemia	MM	multiple myeloma	UPEP	urine protein electrophoresis
G6PD	glucose-6-phosphate dehydrogenase	MPN	myeloproliferative neoplasm	VTE	venous thromboembolism
G-CSF	granulocyte colony-stimulating factor	MPV	mean platelet volume	vWD	von Willebrand disease
GSH	glutathione	NHL	non-Hodgkin lymphoma	vWF	von Willebrand Factor
Hb	hemoglobin	PCC	prothrombin complex concentrates	WBC	white blood cell
Hct	hematocrit	Ph	Philadelphia chromosome	WHO	World Health Organization
HA	hemolytic anemia	PNH	paroxysmal nocturnal hemoglobinuria		
HIT	heparin-induced thrombocytopenia	PV	polycythemia vera		

## Basics of Hematology



**Figure 1. Hematopoiesis**

- over  $10^{11}$  blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies
- lifespan of mature cells in blood:
  - erythrocytes (120 d), neutrophils (~1 d), platelets (10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - spleen: part of reticuloendothelial system, removes aged RBCs, removes antibody-coated bacteria/cells, site of antibody production
  - thymus: site of T-cell maturation, involutes with age
  - lymph nodes: sites of B and T-cell activation (adaptive immune response)



**Erythrocyte:** carries oxygen from lungs to peripheral tissues.

**Reticulocyte:** immature erythrocyte.

**Neutrophil:** granulocyte integral in innate immunity; main cell in acute inflammation.

**Eosinophil:** involved in response to parasites (especially helminths) and allergic response.

**Basophil:** granulocyte mainly involved in allergy and parasitic infection.

**Lymphocyte:** integral cell in adaptive immunity.

**Monocyte:** involved in innate immunity; can differentiate into macrophage or dendritic cell.

**Platelet:** mediator of primary hemostasis.

**Plasma:** liquid component of blood containing water, proteins, coagulation factors and immunoglobulins.

**Serum:** equivalent to plasma minus clotting factors and fibrinogen.

## Complete Blood Count (CBC)

Table 1. Common Terms Found on CBC

Test	Definition	Normal Values*
<b>Red blood cell (RBC) count</b>	The number of RBCs per volume of blood	4.2-6.9 x 10 <sup>6</sup> /mm <sup>3</sup>
<b>Hemoglobin (Hb)</b>	Amount of oxygen-carrying protein in the blood	130-180 g/L (13-18 g/dL) (male) 120-160 g/L (12-16 g/dL) (female)
<b>Hematocrit (Hct)</b>	Percentage of a given volume of whole blood occupied by packed RBCs	45%-62% (male) 37%-48% (female)
<b>Mean corpuscular volume (MCV)</b>	Measurement of size of RBCs	80-100 µm <sup>3</sup>
<b>Mean corpuscular Hb (MCH)</b>	Amount of oxygen-carrying Hb inside RBCs	27-32 pg/cell
<b>Mean corpuscular Hb concentration (MCHC)</b>	Average concentration of Hb inside RBCs	32%-36%
<b>RBC distribution width (RDW)</b>	Measurement of variance in RBC size	11.0%-15.0%
<b>White blood cell (WBC) count</b>	The number of WBCs per volume of blood	4.3-10.8 x 10 <sup>9</sup> /mm <sup>3</sup>
<b>WBC differential</b>	Includes neutrophils, eosinophils, basophils, lymphocytes and monocytes	
<b>Platelet count</b>	The number of platelets per volume of blood	150-400 x 10 <sup>9</sup> /mm <sup>3</sup>
<b>Mean platelet volume (MPV)</b>	Measurement of platelet size	
<b>Reticulocytes</b>	Immature RBCs that contain no nucleus but have residual RNA	Normally make up 1% of total RBC count

\*Normal values may vary depending on site and age

### Approach to Interpreting a CBC

- Consider values in the context of individual's baseline
  - up to 5% of population without disease may have values outside "normal" range
  - an individual may display a clinically significant change from their baseline without violating "normal" reference range
- Is one cell line affected or are several?
  - if all lines are low: pancytopenia (see *Pancytopenia*, H7)
  - if RBCs and platelets are low: consider a microangiopathic hemolytic anemia (MAHA) (see H21)
  - if single cell line affected: see corresponding section in *Common Presenting Problems*, H5

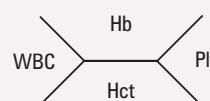


#### Clinical Use of RDW

- To distinguish the etiologies of microcytosis:
  - Iron deficiency: increased RDW (anisocytosis) as cells are of varying sizes in iron deficiency.
  - Thalassemia minor: normal RDW (also expect a high RBC count) as cells are of similar size due to genetic defect in Hb.



#### Complete Blood Count



## Blood Film Interpretation

### RED BLOOD CELLS

#### Size

- microcytic (MCV<80), normocytic (MCV=80-100), macrocytic (MCV>100)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, hemolytic anemias, myelofibrosis, blood transfusion

#### Colour

- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
  - iron deficiency anemia, anemia of chronic disease, sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
  - increased RBC production by bone marrow

#### Shape

- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, myelofibrosis

Table 2. Common Erythrocyte Shapes

Shape	Definition	Associated Conditions
<b>Discocyte</b>	Biconcave disc	Normal RBC
<b>Spherocyte</b>	Spherical RBC (due to loss of membrane)	Hereditary spherocytosis, immune hemolytic anemia, post-transfusion
<b>Elliptocyte/Ovalocyte</b>	Oval-shaped, elongated RBCs <ul style="list-style-type: none"> <li>Elliptocytes: the RBC long axis is ≥2x the length of the short axis</li> <li>Ovalocytes: the RBC long axis is &lt;2x the length of the short axis</li> </ul>	Hereditary elliptocytosis, megaloblastic anemia, myelofibrosis, iron-deficiency, MDS (myelodysplastic syndrome)
<b>Schistocyte (helmet cell)</b>	Fragmented cells (due to traumatic disruption of membrane)	Microangiopathic hemolytic anemia (HUS/TTP, DIC, preeclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, prosthetic heart valve
<b>Sickle cell</b>	Sickle-shaped RBC (due to polymerization of hemoglobin S)	Sickle cell disorders: HbSC, HbSS
<b>Codocyte (target cell)</b>	"Bull's eye" on dried film	Liver disease, hemoglobin SC, thalassemia, Fe deficiency, asplenia
<b>Dacocyte (teardrop cell)</b>	Single pointed end, looks like a teardrop	Myelofibrosis, thalassemia major, megaloblastic anemia

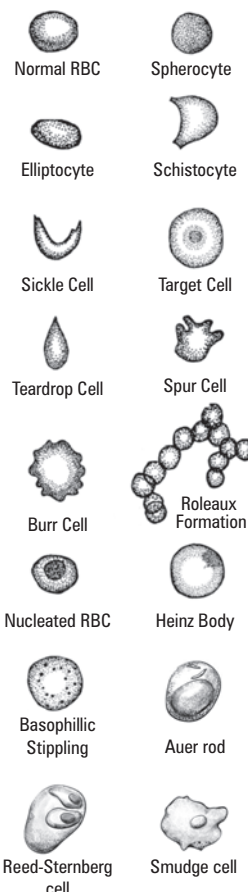


Figure 2. Morphology

**Table 2. Common Erythrocyte Shapes** (continued)

Shape	Definition	Associated Conditions
<b>Acanthocyte (spur cell)</b>	Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids)	Severe liver disease (spur cell anemia), starvation/anorexia, post-splenectomy
<b>Echinocyte (burr cell)</b>	RBC with numerous regularly spaced, small spiny projections	Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, storage artifact
<b>Rouleaux formation</b>	Aggregates of RBC resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)	Pregnancy: most common cause; due to physiological increase in fibrinogen Inflammatory conditions: due to polyclonal immunoglobulins Plasma cell dyscrasias: due to monoclonal paraproteinemia, e.g. multiple myeloma, macroglobulinemia Storage artifact

HUS = Hemolytic uremic syndrome; TTP = Thrombotic thrombocytopenic purpura; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes and low platelets

**Table 3. RBC Inclusions** (see Figure 2)

Inclusions	Definition	Associated Conditions
<b>Nucleus</b>	Present in erythroblasts (immature RBCs)	Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, MPNs (MF)
<b>Heinz bodies</b>	Denatured and precipitated hemoglobin	G6PD deficiency (post-exposure to oxidant), thalassemia, unstable hemoglobins
<b>Howell-Jolly bodies</b>	Small nuclear remnant resembling a pyknotic nucleus	Post-splenectomy, hyposplenism (sickle cell disease), neonates, megaloblastic anemia
<b>Basophilic stippling</b>	Deep blue granulations indicating ribosome aggregation	Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, hereditary (pyrimidine 5'nucleotidase deficiency)
<b>Sideroblasts</b>	Erythrocytes with Fe containing granules in the cytoplasm	Hereditary, idiopathic, drugs, hypothyroidism (see <i>Sideroblastic Anemia</i> , H15), myelodysplastic syndrome

BM = bone marrow; MPN = myeloproliferative neoplasm; MF = myelofibrosis

## WHITE BLOOD CELLS

- lymphocytes: comprise 30-40% of WBCs; great variation in "normal" lymphocyte morphology
  - Reed-Sternberg cell: giant, multinucleated B-lymphocyte, only seen with bone marrow specimens
    - associations: primarily Hodgkin lymphoma, also seen in some non-Hodgkin lymphoma, CLL and EBV infection
  - smudge cells: lymphocytes damaged during blood film preparation indicating cell fragility
    - associations: chronic lymphocytic leukemia (CLL) and other lymphoproliferative disorders – pathognomonic in EBV infection
- neutrophils
  - normally only mature neutrophils (with 3-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
  - hypersegmented neutrophil: >5 lobes suggests megaloblastic process ( $B_{12}$  or folate deficiency)
  - left shift (increased granulocyte precursors)
    - seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, myeloproliferative neoplasms (CML, MF)
- blasts
  - immature, undifferentiated precursors; associated with acute leukemia, MDS, G-CSF (growth factor that stimulates neutrophil production) use
  - Auer rods: clumps of granular material that form long needles in the cytoplasm of myeloblasts
    - pathognomonic for acute myeloid leukemia (AML)

## PLATELETS

- small, purple, anuclear cell fragments



### Left Shift

Refers to an increase in granulocyte precursors in the peripheral smear (myelocytes, metamyelocytes, promyelocytes, blasts). If present, implies increased marrow production of granulocytes (e.g. inflammation, infection, G-CSF administration, CML). The presence of predominantly blasts in the peripheral smear without cells between mature neutrophil and blast suggests clonal cell disorder (MDS, acute leukemias).  
This is a MEDICAL EMERGENCY.



## Bone Marrow Aspiration and Biopsy

- sites: posterior iliac crest, sternum
- possible analyses
  - aspiration: takes a fluid marrow sample for cellular morphology, flow cytometry, cytogenetics, molecular studies, microbiology (C&S, AFB, PCR)
  - biopsy: takes a sample of intact bone marrow to assess histology and immunohistochemistry

### Indications

- unexplained CBC abnormalities
- diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, solid tumours
- diagnosis and staging of lymphoma or solid tumours
- evaluate iron metabolism and stores (gold standard, but rarely done)



- evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher's disease)
- evaluate fever of undetermined origin, suspected mycobacterial, fungal or parasitic infections, or granulomatous disease
- unexplained splenomegaly
- confirm normal bone marrow in potential allogenic hematopoietic cell donor

### Contraindications

- absolute: untreated hemophilia, severe DIC, infection over skin site
- relative: platelet count <10, recent warfarin use with INR >2.0, liver disease with associated coagulopathy
- thrombocytopenia is not a contraindication; may need platelet transfusion prior to procedure

## Common Presenting Problems



### Anemia

#### Definition

- a decrease in red blood cell (RBC) mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
  - adult males: Hb <130 g/L or Hct <0.41
  - adult females: Hb <120 g/L or Hct <0.36

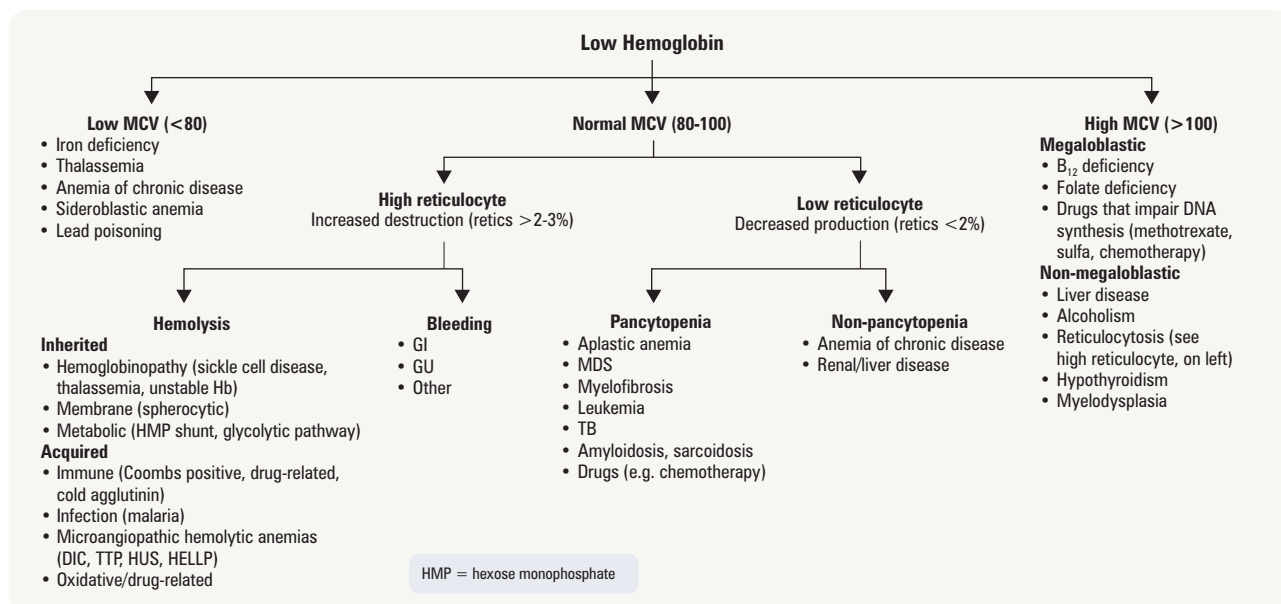


Figure 3. Approach to anemia

#### Clinical Features

- history
  - symptoms of anemia: fatigue, malaise, weakness, dyspnea, decreased exercise tolerance, palpitations, headache, dizziness, tinnitus, syncope
  - acute vs. chronic, bleeding, systemic illness, diet, alcohol, family history
  - menstrual history: menorrhagia, menometrorrhagia, dysfunctional uterine bleeding
  - rule out pancytopenia (recurrent infection, mucosal bleeding/easy bruising)
- physical signs
  - HEENT: pallor in mucous membranes, palmar creases and conjunctiva at Hb <90 g/L (<9 g/dL), ocular bruits at Hb <55 g/L (<5.5 g/dL), angular chelosis, jaundice
  - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
  - dermatologic: pallor in palmar skin creases at Hb <75 g/L, jaundice (if due to hemolysis), nail changes, glossitis

#### Investigations

- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential (MCV, RDW, RBC count)
- reticulocyte count
- blood film
- rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
- additional laboratory investigations as indicated (see *Microcytic Anemia*, H12, *Normocytic Anemia*, H16, *Hemolytic Anemia*, H17 and *Macrocytic Anemia*, H22)



#### Reticulocytes

- Reticulocytes are immature erythrocytes and are markers of erythrocyte production
- Should normally increase when there is a decrease in RBC
- With blood loss, reticulocytes should increase 2-3x initially and then 5-7x over the next week
- A normal reticulocyte count in anemia should be interpreted as a sign of decreased production

## Erythrocytosis



### Definition

- an increase in the number of RBCs: Hb >185 g/L or Hct >52% (males); Hb >165 or Hct >47% (females and African males)

### Etiology

- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, "stress" (Gaisböck's syndrome)
- absolute erythrocytosis

**Table 4. Etiology of Erythrocytosis**

Primary	Secondary	Inappropriate Production of Erythropoietin
Polycythemia Vera (PV) (see H39)	<b>Poor tissue oxygenation/hypoxia:</b> Carbon monoxide poisoning Heavy smoking High altitude <b>Pulmonary disease:</b> COPD Sleep apnea Pulmonary hypertension <b>Cardiovascular disease:</b> R to L shunt (Eisenmenger syndrome) RBC defects (Hb with increased O <sub>2</sub> affinity, methemoglobinemia)	<b>Tumours:</b> Hepatocellular carcinoma Renal cell carcinoma Cerebellar hemangioblastoma Pheochromocytoma Uterine leiomyoma Ovarian tumour <b>Other:</b> Polycystic kidney disease Post-kidney transplant Hydronephrosis Androgens Exogenous erythropoietin

### Clinical Features

- secondary to high red cell mass and hyperviscosity
  - headache, dizziness, tinnitus, visual disturbances, hypertensive symptoms
  - symptoms of angina, congestive heart failure, aquagenic pruritis
- thrombosis (venous or arterial) or bleeding (abnormal platelet function)
- physical findings
  - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

### Investigations

- serum erythropoietin (EPO): increased EPO suggests autonomous production or hypoxia, and is used to rule out PV
  - search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
    - only send if low/normal EPO level
- ferritin (iron deficiency can mask the diagnosis)

### Treatment

- if primary: see PV, H39
- if secondary: treat underlying cause
  - O<sub>2</sub> for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours
  - often cardiologists will not treat high HCT in cyanotic patients (or will have high threshold)

## Thrombocytopenia



### Definition

- platelet count <150 x10<sup>9</sup>/L

### Clinical Features

- history: bleeding gums, epistaxis, bleeding post-surgical procedures, metromenorrhagia
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura
  - hemarthrosis and deep muscle hematomas are rarely initial signs in patients with primary hemostatic disorders
- see *Disorders of Primary Hemostasis*, H25, for complications

### Investigations

- CBC and differential
- blood film
  - decreased production: other cell line abnormalities, blasts, hypersegmented PMNs, leukoerythroblastic changes
  - increased destruction: large platelets, schistocytes (seen in MAHA)
  - rule out platelet clumping
- work-up for nutritional deficiencies: B<sub>12</sub>, RBC folate
- PT/INR, aPTT and fibrinogen if DIC suspected
- LFTs

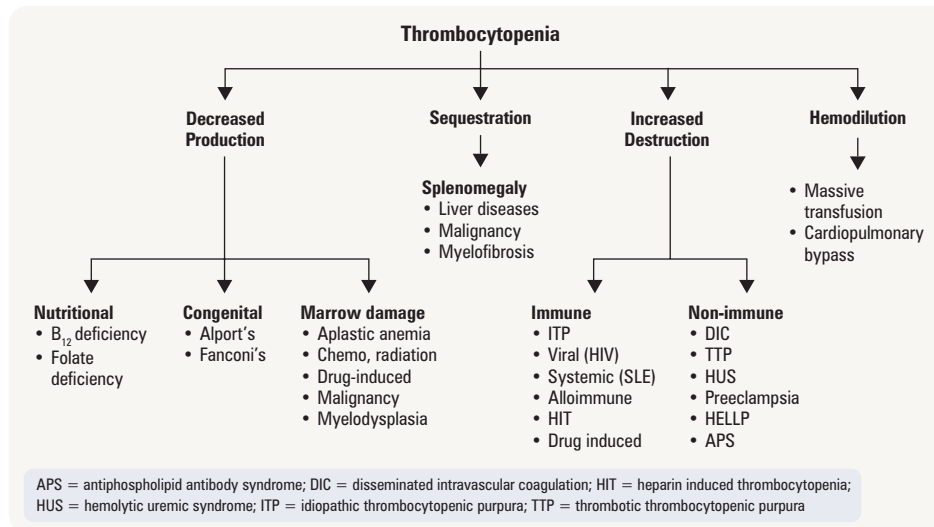


#### Must rule out factitious

**thrombocytopenia:** platelet clumping (secondary to EDTA antibodies from collection tube). This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA).

### Treatments

- life threatening bleed: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see *ITP*, H26



### References

APS: see [Hematology](#), H34  
 Aplastic Anemia: see [Hematology](#), H16  
 B<sub>12</sub>/Folate Deficiency: see [Hematology](#), H22/H23  
 DIC: see [Hematology](#), H30  
 HELLP: see [Obstetrics](#), OB19  
 HIT: see [Hematology](#), H27  
 HIV: see [Infectious Diseases](#), ID41  
 ITP: see [Hematology](#), H26  
 Myelodysplasia: see [Hematology](#), H36  
 Preeclampsia: see [Obstetrics](#), OB16  
 SLE: see [Rheumatology](#), RH11

Figure 4. Approach to thrombocytopenia

Adapted from Cecil's Essentials of Medicine

## Thrombocytosis

### Definition

- platelet count  $>400 \times 10^9/L$
- primary thrombocytosis: due to myeloproliferative neoplasms [e.g. CML, polycythemia vera (PV), primary myelofibrosis, essential thrombocytosis (ET). Rarely associated with MDS]
- reactive/secondary thrombocytosis: acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms, ischemic injury); much more common than primary

### Clinical Features

- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative neoplasms (MPNs)

### Investigations

- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS

### Treatment

- primary: ASA  $\pm$  cytoreductive agents
- secondary: treat underlying cause

## Pancytopenia



### Definition

- a decrease in all hematopoietic cell lines

### Clinical Features

- anemia: fatigue
- leukopenia: recurrent infections
- thrombocytopenia: mucosal bleeding and ecchymoses

### Investigations

- CBC and differential, blood film
- reticulocyte count
- investigate secondary causes as per history: HIV test, serum B<sub>12</sub>, RBC folate, ANA
  - on history, inquire about drug (including OTC/herbal) and environmental exposures
- often requires bone marrow biopsy to determine cause

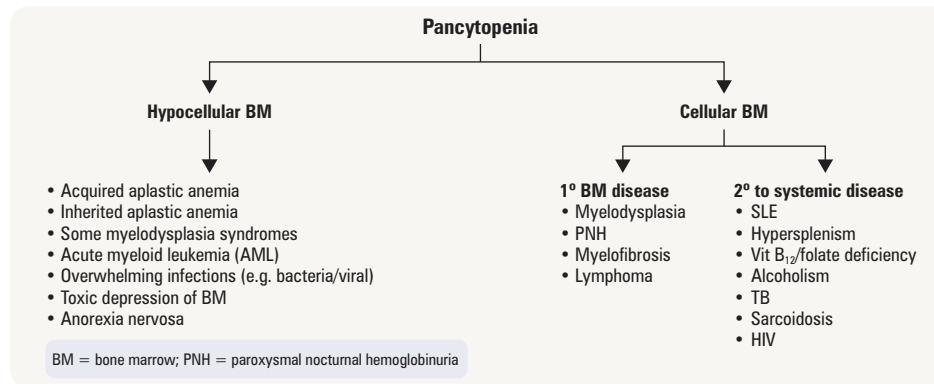


Figure 5. Approach to pancytopenia

## Neutrophilia

### Definition

- different guidelines, but absolute neutrophil count (ANC)  $>7.7 \times 10^9/L$

### Etiology

- primary neutrophilia
  - chronic myeloid leukemia (CML)
  - other myeloproliferative disorders: PV, essential thrombocytosis (ET), myelofibrosis
  - hereditary neutrophilia (autosomal dominant)
  - chronic idiopathic neutrophilia in otherwise healthy patients leukocyte adhesion deficiency
- secondary neutrophilia
  - smoking: most common cause of mild neutrophilia
  - infection: leukocytosis with left shift  $\pm$  toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
  - inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, burns
  - malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  - stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  - medications: glucocorticoids,  $\beta$ -agonists (e.g. epinephrine), lithium

### Clinical Features

- look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  - including lymph nodes and organomegaly
- examine oral cavity, teeth, peri-rectal area, genitals and skin for signs of infection

### Investigations

- CBC and differential: mature neutrophils or bands  $>20\%$  of total WBC suggests infection/inflammation
- blood film: Döhle bodies, toxic granulation, cytoplasmic vacuoles in infection
- review other blood counts
- may require bone marrow biopsy if MPN suspected

### Treatment

- directed at underlying cause

## Neutropenia

### Definition

- mild: ANC  $1.0\text{--}1.5 \times 10^9/L$
- moderate: ANC  $0.5\text{--}1.0 \times 10^9/L$  (risk of infection starts to increase)
- severe: ANC  $<0.5 \times 10^9/L$
- profound: ANC  $<0.1 \times 10^9/L$  for  $>7$  d



Absolute Neutrophil Count (ANC) =  
WBC count  $\times$  (%PMNs + %bands)

Beware of fever + ANC  $<0.5 \times 10^9/L$  =  
FEBRILE NEUTROPENIA

## Etiology

**Table 5. Etiology of Neutropenia**

Decreased Production	Peripheral Destruction	Excessive Margination (Transient Neutropenia)
<b>Infection:</b> Viral hepatitis, EBV, HIV, TB, typhoid, malaria <b>Hematological diseases:</b> Idiopathic, aplastic anemia, myelofibrosis, BM infiltration <b>Drug-induced:</b> Alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, anti thyroid drugs <b>Toxins/Chemicals:</b> High dose radiation, benzene, DDT <b>Nutritional Deficiency:</b> B <sub>12</sub> , folate <b>Idiopathic:</b> Constitutional neutropenia, benign cyclic neutropenia, cyclical	Anti-neutrophil antibodies Spleen or lung trapping Autoimmune disorders: RA, SLE Granulomatosis with polyangiitis (formerly Wegener's) Drugs: haptens (e.g. $\alpha$ -methyl dopa)	Idiopathic (most common) Overwhelming bacterial infection Hemodialysis Racial variation (e.g. African or Ashkenazi Jewish descent)

### Clinical Features

- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. *S. aureus*, gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth and throat following colonization by opportunistic organisms
- avoid digital rectal exam

### Investigations

- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

### Treatment

- regular dental care: chronic gingivitis and recurrent stomatitis major sources of morbidity
- febrile neutropenia (see [Infectious Diseases](#), ID39)
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, methotrexate)



#### Prophylactic Hematopoietic Colony-Stimulating Factors on Mortality and Infection

*Ann Intern Med* 2007;147:400-411

**Purpose:** To review the effects of colony-stimulating factor (CSF) on mortality, infections, and febrile neutropenia in patients undergoing chemotherapy or stem-cell transplant (SCT).

**Study Selection:** 148 RCTs comparing the effects of CSFs to either placebo or no therapy were included. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.

**Results:** There were no differences in all-cause mortality or infection-related death between CSF and placebo groups. Compared to placebo or no therapy, CSFs reduced infection rate (median rate 38.9% vs. 43.1%; rate ratio 0.85), microbiologically documented infections (MR 23.5% vs. 28.6%; rate ratio 0.86), and febrile neutropenia (MR 25.3% vs. 44.2%; rate ratio 0.71).

**Conclusions:** Prophylactic CSFs decrease infection rates and episodes of febrile neutropenia in patients undergoing chemotherapy or SCT, but have no effect on mortality.



**G-CSF = Neupogen® = Filgrastim**

## Lymphocytosis

### Definition

- absolute lymphocyte count  $>4 \times 10^9/L$

### Etiology

- infection
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
- physiologic response to stress (e.g. trauma, status epilepticus)
- hypersensitivity (e.g. drugs, serum sickness)
- autoimmune (e.g. rheumatoid arthritis)
- neoplasm (e.g. ALL, CLL, lymphoma)

### Investigations

- peripheral smear

### Treatment

- treat underlying cause



Presence of smudge cells suggests a lymphoproliferative disorder if persistently elevated above  $5.0 \times 10^9/L$  for  $>3$  mo. Consider flow cytometry.



Presence of atypical lymphocytes suggests viral infection.

## Lymphopenia

### Definition

- absolute lymphocyte count  $<1.5 \times 10^9/L$

### Etiology

- idiopathic CD4+ lymphocytopenia
- radiation
- HIV/AIDS, hepatitis B, hepatitis C
- malignancy/chemotherapeutic agents
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)

**Clinical Features**

- opportunistic infections (see [Infectious Diseases](#), ID39)

**Treatment**

- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see [Infectious Diseases](#), ID47)



## Eosinophilia

**Definition**

- absolute eosinophil count  $>0.5 \times 10^9/L$

**Etiology**

- primary: due to clonal bone marrow disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome
    - ♦ 6 mo of eosinophilia with no other detectable causes
    - ♦ can involve heart, bone marrow, CNS
- secondary:
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes:
    - ♦ polyarteritis nodosa, see [Rheumatology](#), RH19
    - ♦ respiratory causes (asthma, eosinophilic pneumonia, Churg-Strauss)
    - ♦ cholesterol emboli
    - ♦ hematologic malignancy: CML, Hodgkin lymphoma, see H38, H43
    - ♦ adrenal insufficiency, see [Endocrinology](#), E35
    - ♦ medications (penicillins)

**Basophilia and/or Eosinophilia**

Can be an indicator of chronic myeloid leukemia or other myeloproliferative neoplasm, associated with pruritus due to excessive histamine production.

**Treatment**

- treat underlying cause

## Agranulocytosis

**Definition**

- severe depletion of granulocytes (neutrophils, eosinophils, basophils) from the blood and granulocyte precursors from bone marrow

**Etiology**

- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors

**Clinical Features**

- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

**Prognosis**

- high fatality without vigorous treatment

**Investigations/Treatment**

- discontinue offending drug
- pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider bone marrow aspirate and biopsy if cause unclear
- consider G-CSF

## Leukemoid Reactions

- blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
- leukocytosis  $>50 \times 10^9/L$ , marked left shift (myelocytes, metamyelocytes, bands in peripheral blood smear)

**Etiology**

- important to rule out CML
- differential diagnosis:
  - myeloid progenitors: pneumonia, other acute bacterial infections, intoxications, burns, malignant disease, severe hemorrhage or hemolysis
  - lymphoid progenitors: pertussis, TB, infectious mononucleosis
- monocytic progenitors: TB



# Approach to Lymphadenopathy

## History

- constitutional/B-symptoms: seen in TB, lymphoma, other malignancies
- exposures: cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), high risk behaviors (HIV)
- joint pain/swelling, rashes (connective tissue disorder)
- pruritus (seen in Hodgkin lymphoma)
- medications (can cause serum sickness → lymphadenopathy)

## Physical Exam

- basic assessment: occipital, preauricular, submandibular, cervical, supra/infra-clavicular, axillary, epitrochlear, inguinal, popliteal nodes
  - characteristics of lymph nodes (see Table 6)
  - look for signs of infection in regions which lymph nodes drain
- determine if lymphadenopathy is localized or generalized
- localized: typically reactive or neoplastic
  - cervical (bacterial/mycobacterial infections, ENT malignancies, metastatic cancer)
  - supraclavicular
    - ♦ right (mediastinal, bronchogenic, esophageal cancer)
    - ♦ left (gastric, gall bladder, pancreas, renal, testicular/ovarian cancer)
  - axillary (cat scratch fever, breast cancer, metastatic cancer)
  - epitrochlear (infections, sarcoidosis, lymphoma)
  - lower/inguinal (STDs, skin, cervix, vulva/penis, rectum/anus cancer)
- generalized: see Table 7
- thorough examination required to assess for systemic disease

## Investigations

- CBC and differential, blood film
- ± tuberculin test, HIV RNA, RPR/VDRL, monospot/EBV serology, ANA, imaging as indicated
- if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → biopsy)
- excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
- in difficult to access areas (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
- FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (use excisional biopsy instead)
  - helpful for recurrence of solid tumour malignancy

**Table 6. Inflammatory vs. Neoplastic Lymph Nodes**

Feature	Inflammatory	Neoplastic
Consistency	Rubbery	Firm/hard
Mobility	Mobile	Matted/Immobile
Tenderness	Tender	Non-tender
Size	<2 cm	>2 cm

\*Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender

**Table 7. Differential Diagnosis of Generalized Lymphadenopathy**

Reactive	Inflammatory	Neoplastic
Bacterial (TB, Lyme, brucellosis, cat-scratch disease), syphilis)	Collagen disease (RA, dermatomyositis, SLE, vasculitis, Sjögren)	Lymphoproliferative disorder/Lymphoma
Viral (EBV, CMV, HIV)	Drug hypersensitivity	Metastatic cancer
Parasitic (toxoplasmosis)	Sarcoidosis, amyloidosis	Histiocytosis X
Fungal (histoplasmosis)	Serum sickness	



### B-symptoms

- Unexplained temperature >38°C
- Unexplained weight loss (>10% of body weight in 6 mo)
- Night sweats



### Drugs That Can Cause Lymphadenopathy

- Allopurinol
- Atenolol
- Captopril
- Carbamazepine
- Cephalosporins
- Gold
- Hydralazine
- Penicillin
- Phenytoin
- Primidone
- Pyrimethamine
- Quinidine
- Sulfonamides

## Approach to Splenomegaly



**Table 8. Differential Diagnosis of Splenomegaly**

Increased Demand for Splenic Function			Congestive	Infiltrative
<b>Hematological</b>	<b>Infectious</b>	<b>Inflammatory</b>	<b>Cirrhosis</b>	<b>Non-malignant</b>
Spherocytosis	CMV	Felty syndrome	Splenic vein thrombosis	Benign metaplasia
Hemoglobinopathies	Bacterial endocarditis	Still's disease	Portal vein obstruction	Amyloidosis, Sarcoidosis
Hemolysis	TB	SLE	Portal HTN (including right heart failure)	<u>Lysosomal storage diseases</u>
Sequestration crisis	<u>HIV/AIDS</u>	Sarcoidosis		(Gaucher's, Niemann-Pick)
Nutritional anemias	EBV			Glycogen storage diseases
Elliptocytosis	<u>Malaria</u>			Hamartomas
	Histoplasmosis			Cysts
	<u>Leishmaniasis</u>			Vascular abnormalities
				<b>Malignant</b>
				<u>Leukemia (CML, CLL)</u>
				<u>Lymphoproliferative disease</u>
				<u>Hodgkin lymphoma</u>
				<u>Myeloproliferative disorders</u>
				Metastatic tumour

The underlined conditions cause massive splenomegaly (spleen crosses midline or reaches pelvis)

### History

- constitutional symptoms, feeling of fullness in LUQ
- signs or symptoms of infection or malignancy
- history of liver disease, hemolytic anemia or high-risk exposures

### Physical Exam

- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell's sign, Traube's space, Nixon's method) and palpation
- associated lymphadenopathy or hepatomegaly
- signs of CHF

### Investigations

- CBC and differential, blood film
- as indicated: liver enzymes/liver function tests, reticulocyte count, Monospot®, haptoglobin, LDH, infectious and autoimmune workups
- imaging
  - ultrasound of abdomen/liver to rule out cirrhosis and portal vein thrombosis
  - echo for cardiac function
  - CT to rule out lymphoma



#### Causes of Splenomegaly

##### CHINA

Cirrhosis/Congestion (portal HTN)

Hematological

Infectious

Neoplasm (malignant, non-malignant)

Autoimmune



#### Does this Adult Patient have Splenomegaly?

From The Rational Clinical Examination  
JAMA 2009; <http://www.jamaevidence.com/content/3487298>

**Study:** Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for detecting splenomegaly.

**Results:** On percussion, Nixon sign had a positive likelihood ratio (+LR) of 3.6 (95% CI, 1.8-7.3) and a negative likelihood ratio (-LR) of 0.41 (95% CI, 0.26-0.64). Percussion of Traube's space had a +LR of 2.3 (95% CI, 1.8-2.9) and -LR of 0.48 (95% CI, 0.39-0.60), while Castell sign had a +LR of 1.2 (95% CI, 0.98-1.6) and -LR of 0.45 (95% CI, 0.19-1.1). On palpation, supine 1-handed palpation had a +LR of 8.2 (95% CI, 5.8-1.2) and -LR of 0.41 (95% CI, 0.30-0.57). Middleton hooking maneuver had a +LR of 6.5 (95% CI, 3.1-1.5) and -LR of 0.16 (95% CI, 0.08-0.32).

**Conclusions:** Palpation may have greater accuracy than percussion, but may be best when both are used in tandem. Specifically, Nixon sign and supine 1-handed palpation are the most accurate, respectively.

## Microcytic Anemia



- MCV <80 fL
- see Figure 3, *Approach to Anemia*, H5

**Table 9. Iron Indices and Blood Film in Microcytic Anemia (MCV <80)**

	Lab Tests				Blood Film
	Ferritin	Serum Iron	TIBC	RDW	
<b>Iron Deficiency Anemia</b>	↓↓	↓	↑	↑ (>15)	• Hypochromic, microcytic
<b>Anemia of Chronic Disease</b>	N/↑	↓	↓	N	• Normocytic/microcytic
<b>Sideroblastic Anemia</b>	N/↑	↑	N	↑	• Dual population • Basophilic stippling
<b>Thalassemia</b>	N/↑	N/↑	N	N/↑	• Hypochromic, microcytic • Basophilic stippling • Poikilocytosis

TIBC = total iron-binding capacity



#### Causes of Microcytic Anemia

##### TAILS

Thalassemia

Anemia of chronic disease

Iron deficiency

Lead poisoning

Sideroblastic anemia

## Iron Metabolism



### Iron Intake (Dietary)

- average North American adult diet = 10-20 mg iron (Fe) daily
- absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males have positive Fe balance; up to 20% of menstruating females have negative Fe balance

**Iron Indices** (see Table 9 and Figure 6)

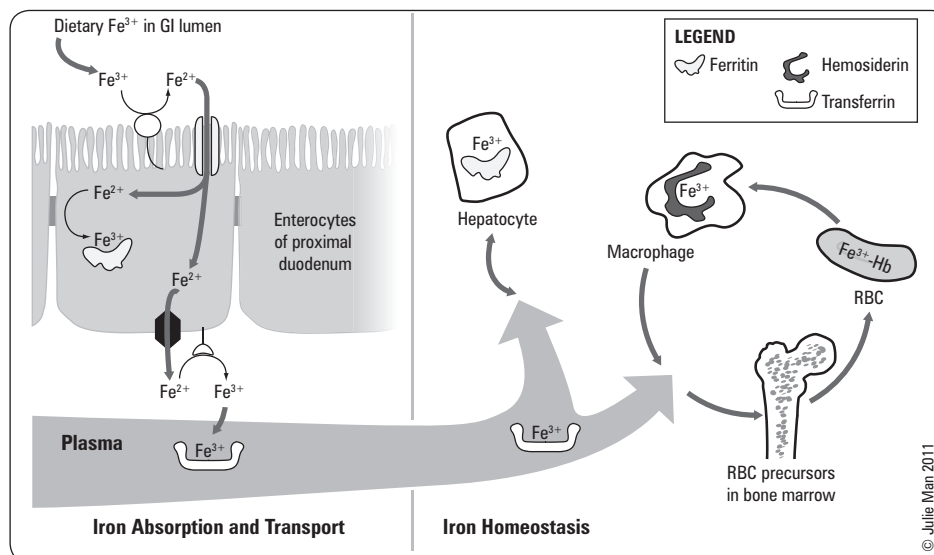
- bone marrow aspirate: gold standard test for iron stores (rarely done)
- serum ferritin: most important blood test for iron stores
  - decreased in iron deficiency anemia
  - elevated in:
    - ♦ infection, inflammation, malignancy
    - ♦ liver disease, hyperthyroidism and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
  - virtually all serum iron is bound to transferrin, only a trace is free or complexed in ferritin
- total iron binding capacity (TIBC): total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - high specificity for decreased iron, low sensitivity
- saturation:
  - serum Fe divided by TIBC, expressed as a proportion or a percentage
  - low in iron deficiency anemia
- soluble transferrin receptor (sTfR):
  - reflects the availability of iron at the tissue level
  - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some is cleaved off and is present in circulation as sTfR
  - in iron deficient states more transferrin receptor is expressed on erythroblasts leading to an increase in sTfR
  - low in reduced erythropoiesis and iron overload
  - useful in determining iron deficiency in the setting of chronic inflammatory disorders (see *Iron Deficiency Anemia*, H14)

**Iron Absorption and Transport** (see Figure 6)

- dietary iron is absorbed in the duodenum (impaired by IBD, celiac disease, etc.)
- in circulation the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages and hepatocytes) to RBC precursors in the bone marrow

**Iron Storage**

- ferritin
  - ferric iron ( $\text{Fe}^{3+}$ ) complexed to a protein called apoferritin (hepatocytes are main ferritin storage site)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated despite low Fe stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is main source of hemosiderin storage

**Figure 6. Iron metabolism**

## Iron Deficiency Anemia

- see [Pediatrics](#), P47
- most common cause of anemia in North America

### Etiology

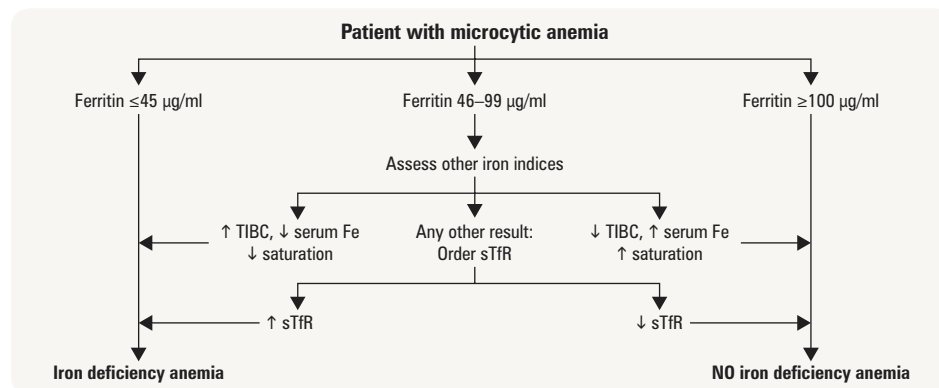
- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology)
  - cow's milk (infant diet)
  - "tea and toast" diet (elderly)
  - absorption imbalances
  - post-gastrectomy
  - malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis)
- increased losses
  - hemorrhage
    - ♦ obvious causes: menorrhagia, abnormal uterine bleeding, frank GI bleed
    - ♦ occult: peptic ulcer disease, GI cancer
  - hemolysis
    - ♦ intravascular (e.g. paroxysmal nocturnal hemoglobinuria (PNH), cardiac valve RBC fragmentation)
    - ♦ extravascular (e.g. immune hemolytic anemias)

### Clinical Features

- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see *Approach to Anemia*, H5
- brittle hair, nail changes (brittle, koilonychia)
- Plummer-Vinson syndrome: dysphagia (esophageal webs), glossitis, angular stomatitis (inflammation and fissuring at the corners of the mouth)
- pica (appetite for non-food substances e.g. ice, paint, dirt)

### Investigations

- iron indices, including soluble transferrin receptor (Figure 7)
  - low ferritin (<45 µg/L) is diagnostic of iron deficiency (Table 10)
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup (Figure 7)
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms, anisocytosis
  - target cells (thin)
- bone marrow (gold standard but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation



**Figure 7. Approach to interpreting iron indices**

Adapted from Am Fam Physician 2007;75:671-678

### Treatment

- treat underlying cause
- supplementation
  - oral (tablets, syrup)
    - ♦ ferrous sulphate 325 mg tid, ferrous gluconate 300 mg tid, or ferrous fumarate 300 mg tid
    - ♦ supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - ♦ oral iron should be taken with citrus juice to enhance absorption
  - IV (iron sucrose or dextran) can be used if patient cannot tolerate or absorb oral iron



#### Plummer-Vinson Syndrome Triad

- Dysphagia (esophageal)
- Glossitis
- Iron deficiency anemia

**Table 10. The Utility of Ferritin in the Diagnosis of Iron Deficiency Anemia**

Ferritin (µg/L)	Likelihood ratio for iron deficiency anemia
>100	0.13
45-100	0.46
18-45	3.12
≤18	41.47

Am J Med 1990;88:205-209



Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.).

In males and in post-menopausal women a GI work-up is always warranted.

- monitoring response
  - reticulocyte count will begin to increase after one wk
  - Hb normalizes by 10 g/L per wk (if no blood loss)
  - iron supplementation required for 4-6 mo to replenish stores

## Anemia of Chronic Disease

- see [Pediatrics](#), P48

### Etiology

- infection, malignancy, inflammatory and rheumatologic disease, chronic renal and liver disease, endocrine disorders (e.g. diabetes mellitus, hypothyroidism, hypogonadism, hypopituitarism)

### Pathophysiology

- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - enterocyte trapping of iron → increased hepcidin inhibits ferroportin (↓ iron into circulation)
  - macrophage trapping of iron → reduced plasma iron levels making iron relatively unavailable for new hemoglobin synthesis
  - marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present
- RBC survival is modestly decreased

### Investigations

- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen)
- “classic” serum iron indices (see Table 9)
  - serum iron and TIBC low, % saturation normal
  - serum ferritin is normal or increased
- anemia of chronic disease often co-exists with iron deficiency (see sidebar)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- bone marrow
  - normal or increased iron stores
  - decreased or absent staining for iron in erythroid precursors

### Treatment

- treat underlying disease
- only treat anemia in patients who can benefit from a higher hemoglobin
- IV iron if no benefit from PO iron
- erythropoietin indicated in chronic renal failure. Not to be used if patient has concomitant curative solid tumour malignancy. Ensure Hb target <110 g/L



**Iron-deficiency anemia commonly co-exists with anemia of chronic disease. Suggested by:**

- Serum ferritin <100 µg/L in setting of a chronic inflammatory disease
- Elevation of soluble transferrin receptor
- Absence of stainable iron on bone marrow aspiration/biopsy
- Response to a therapeutic trial of oral iron

## Sideroblastic Anemia



- uncommon compared to iron deficiency anemia or anemia of chronic disease

### Sideroblasts

- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
- “normal”: granules are small, randomly spread in the cytoplasm
  - found in healthy individuals
- “ring”: iron deposits in mitochondria, forming a ring around the nucleus
  - abnormal, large granules
  - the hallmark of sideroblastic anemia

### Etiology

- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - aka refractory anemia with ringed sideroblasts: a subtype of MDS (see *Myelodysplastic Syndromes*, H36)
  - may be a preleukemic phenomenon (10% transform to AML)
- reversible
  - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, hypothyroidism

**Clinical Features**

- anemia symptoms (see *Approach to Anemia*, H5)
- hepatosplenomegaly,  $\text{Fe}^{2+}$  overload syndrome

**Investigations**

- serum iron indices
  - increased serum  $\text{Fe}^{2+}$ , normal TIBC, increased ferritin, increased sTfR
- blood film/bone marrow biopsy
  - ringed sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikilocytosis, basophilic stippling

**Treatment**

- depends on etiology
  - X-linked: high dose pyridoxine (vitamin B<sub>6</sub>) in some cases
  - acquired: EPO and G-CSF
  - reversible: remove precipitating cause
- supportive transfusions for severe anemia



Consider lead poisoning in any child microcytic anemia who lives in a house built before 1977.

**Features of Lead Poisoning****LEAD**

Lead lines on gingivae and epiphyses of long bones on x-ray  
 Encephalopathy and Erythrocyte basophilic stippling  
 Abdominal colic and microcytic Anemia (sideroblastic)  
 Drops (wrist and foot drop)

**Causes of Normocytic Anemia****ABCD**

Acute blood loss  
 Bone marrow failure  
 Chronic disease  
 Destruction (hemolysis)

## Lead Poisoning

**Definition/Etiology**

- blood lead levels greater than 80  $\mu\text{g}/\text{dL}$ , possible symptomatology at 50  $\mu\text{g}/\text{dL}$

**Clinical Features**

- identify source: consider occupational history, exposures history
- abdominal pain, constipation, irritability, difficulty concentrating

**Treatment**

- chelation therapy: dimercaprol and EDTA are first line agents

## Thalassemia

- see *Hemolytic Anemia – Thalassemia*, H18

## Normocytic Anemia

- MCV 80-100 fL
- see Figure 3, *Approach to Anemia*, H5

## Aplastic Anemia

**Definition**

- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

**Epidemiology**

- occurs at any age
- slightly more common in males

**Etiology**

**Table 11. Etiology of Aplastic Anemia**

Congenital	Acquired
Fanconi's anemia Shwachman-Diamond syndrome	<b>Idiopathic</b> Often T-cell mediated <b>Drugs</b> Dose-related (i.e. chemotherapeutics) Idiosyncratic (chloramphenicol, phenylbutazone) <b>Toxins</b> Benzene/organic solvents DDT, insecticides
	<b>Ionizing Radiation</b> <b>Post-viral infection</b> Parvovirus B19, EBV, HDV, HEV, HBV, HHV6, HIV <b>Autoimmune (rare)</b> SLE, Graft-versus-host disease <b>Others</b> PNH, pregnancy, anorexia nervosa, thymoma

**Clinical Features**

- can present acutely or insidiously
- symptoms of anemia (see *Approach to Anemia*, H5), thrombocytopenia (see *Thrombocytopenia*, H6) and/or infection
- $\pm$  splenomegaly and lymphadenopathy (depending on the cause)



### Investigations

- exclude other causes of pancytopenia (Figure 3)
- CBC
  - anemia or neutropenia or thrombocytopenia (any combination)  $\pm$  pancytopenia
  - decreased reticulocytes ( $<1\%$  of the total RBC count)
- blood film
  - decreased number of normal RBCs
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement
  - decreased cellularity

### Treatment

- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
  - judicious use so as to not increase the risk of immune sensitization to blood products
- immunosuppression
  - anti-thymocyte globulin: 50-60% of patients respond
  - cyclosporine
- allogenic bone marrow transplant

## Hemolytic Anemia (HA)



### Classification

- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
  - immune
    - ♦ hemolytic transfusion reaction, autoimmune HA (AIHA), drugs (e.g. penicillin), cold agglutinins
    - ♦ alloimmune (transfusion reaction, hemolytic disease of the fetus/newborn)
  - non-immune
    - ♦ microangiopathic HA (MAHA): thrombus in blood vessel causes RBCs to be sheared – associated with DIC, HUS/TTP, preeclampsia/HELLP, vasculitides, malignant hypertension
    - ♦ other causes: paroxysmal nocturnal hemoglobinuria (PNH), hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, mechanical heart valves
- also classified as intravascular or extravascular:
  - intravascular: G6PD deficiency, TTP, DIC and PNH
  - extravascular: AIHA and hereditary spherocytosis

### Clinical Features Specific to HA

- jaundice
- dark urine (hemoglobinuria, bilirubin)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

### Investigations

Table 12. Investigations for Hemolytic Anemia

Screening Tests	Tests Specific For Intravascular Hemolysis
Increased LDH	Schistocytes on blood film
Decreased haptoglobin	Free hemoglobin in serum
Increased unconjugated bilirubin	Methemalbuminemia (heme + albumin)
Increased urobilinogen	Hemoglobinuria (immediate)
Reticulocytosis	Hemosiderinuria (delayed)
	Plasma hemoglobin
Tests Specific for Extravascular Hemolysis	
Direct Coombs test (direct antiglobulin test)	
• Detects IgG or complement on the surface of RBC	
• Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination	
• Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction	
Indirect Coombs test (indirect antiglobulin test)	
• Detects antibodies in serum that can recognize antigens on RBCs	
• Mix patient's serum + donor RBCs + Coombs' serum (anti-human Ig Ab); positive if agglutination	
• Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA	



#### Laboratory Findings in HA

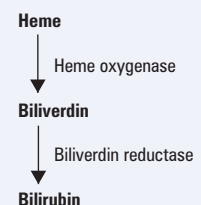
- $\uparrow$  retics
- $\downarrow$  haptoglobin
- $\uparrow$  unconj. bilirubin
- $\uparrow$  urobilinogen
- $\uparrow$  LDH



Disruption of the heme breakdown pathway causes the **porphyria** disorders.



#### Heme Breakdown



## Thalassemia

### Definition

- defects in production of the  $\alpha$  or  $\beta$  chains of hemoglobin
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
- clinical manifestations and treatment depends on specific gene and number of alleles affected
- common features:
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film

### Pathophysiology

- defect may be in any of the Hb genes
  - normally 4 $\alpha$  genes in total; 2 on each copy of chromosome 16
  - normally 2 $\beta$  genes in total; 1 on each copy of chromosome 11
  - fetal hemoglobin, HbF ( $\alpha_2\gamma_2$ ), switches to adult forms HbA ( $\alpha_2\beta_2$ ) and HbA<sub>2</sub> ( $\alpha_2\delta_2$ ) at 3-6 mo of life
  - HbA constitutes 97% of adult hemoglobin
  - HbA<sub>2</sub> constitutes 3% of adult hemoglobin



#### ThalasSEAmia

$\beta$ -Thal → prevalent in Mediterranean

$\alpha$ -Thal → prevalent in **South East Asia (SEA)** and Africa ( $\alpha$  = Asia, Africa)

## $\beta$ -Thalassemia Minor (Thalassemia Trait)

### Definition

- defect in single allele of  $\beta$  gene (heterozygous)
- common in people of Mediterranean and Asian descent

### Clinical Features

- None; a palpable spleen is very rare

### Investigations

- Hb 100-140 g/L or 9-14 g/dL, MCV < 70, normal Fe, normal RBC count
- peripheral blood film – microcytosis basophilic stippling
- Hb electrophoresis
  - specific: HbA<sub>2</sub> increased to 2.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

### Treatment

- no treatment required
- genetic counselling for patient and family



#### Microcytosis in $\beta$ -Thal Minor

Microcytosis is much more profound and the anemia is much milder than that of iron deficiency.

## $\beta$ -Thalassemia Major

### Definition

- defect in both alleles of  $\beta$  gene (homozygous, autosomal recessive)

### Pathophysiology

- ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs and increase in HbF

### Clinical Features

- initial presentation at age 6-12 mo when HbA normally replaces HbF
  - severe anemia, jaundice
- stunted growth and development (hypogonadal dwarf)
- gross hepatosplenomegaly (due to extramedullary hematopoiesis)
- radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
  - skull x-ray has “hair-on-end” appearance
  - pathologic fractures common
- evidence of increased Hb catabolism (e.g. pigmented gallstones)
- death can result from
  - untreated anemia (should transfuse)
  - infection (should identify and treat early)
  - iron overload: late complication secondary to repeated transfusions and ineffective erythropoiesis

### Investigations

- CBC: Hb 40-60 g/L (4-6 g/dL)
- Hb electrophoresis
  - HbA: 0-10% (normal >95%)
  - HbA<sub>2</sub> >2.5%
  - HbF: 90-100%

### Treatment

- lifelong regular transfusions to suppress endogenous erythropoiesis
- iron chelation (e.g. deferoxamine, deferasirox, deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)
- folic acid supplementation if not transfused
- allogenic bone marrow transplantation
- splenectomy (now performed less frequently)

## α-Thalassemia

### Definition

- defect(s) in α genes
- similar geographic distribution as β-thalassemia, but higher frequency among Asians and Africans

### Clinical Features

- 1 defective α gene: clinically silent; normal Hb, normal MCV
- 2 defective α genes: decreased MCV, normal Hb
- 3 defective α genes: HbH (β<sub>4</sub>) disease; presents in adults, decreased MCV, decreased Hb, splenomegaly
- 4 defective α genes: Hb Barts (γ<sub>4</sub>) disease (hydrops fetalis); usually incompatible with life

### Investigations

- peripheral blood film – screen for HbH inclusion bodies with special stain
- Hb electrophoresis not diagnostic for α-thalassemia
- DNA analysis using α gene probes is the only way to confirm the diagnosis

### Treatment

- depends on degree of anemia:
  - 1 or 2 defective α genes: no treatment required
  - HbH disease: similar to β-thalassemia intermedia
  - HbBarts: intrauterine transfusion

## Sickle Cell Disease

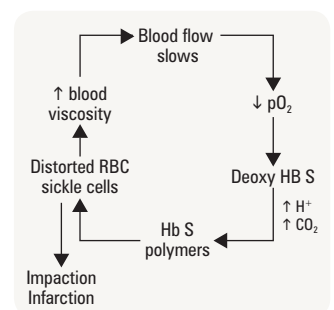
- see [Pediatrics](#), P48

### Definition

- sickling disorders arise due to a mutant β-globin chain, most commonly caused by a Glu → Val substitution at position 6 (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)
  - increased incidence of HbS allele with African or Mediterranean heritage (thought to be protective against malaria)
- sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

### Pathophysiology (Figure 8)

- at low pO<sub>2</sub>, deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes → 'sickles'
- the pO<sub>2</sub> level at which sickling occurs is related to the percentage of HbS present
  - heterozygotes (HbAS); sickling occurs at a pO<sub>2</sub> of 40 mmHg
  - homozygotes (HbSS); sickling occurs at a pO<sub>2</sub> of 80 mmHg
- sickling aggravated by acidemia, increased CO<sub>2</sub>, increased 2,3-DPG, fever and osmolality
- fragile sickle cells hemolyze (nitric oxide depletion); they also occlude small vessels (ischemia-reperfusion injury)



**Figure 8. Pathophysiology of sickling**



**Functional asplenism:** increased susceptibility to infection by encapsulated organisms

- *S. pneumoniae*
- *N. meningitidis*
- *H. influenzae*
- *Salmonella* (osteomyelitis)



#### Acute Chest Syndrome

Affects 30% of patients with sickle cell disease and may be life threatening. Presentation includes dyspnea, chest pain, fever, tachypnea, leukocytosis, and pulmonary infiltrate on CXR. Caused by vaso-occlusion, infection, or pulmonary fat embolus from infarcted marrow.

### Clinical Features

- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection
  - increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - retarded growth and development ± skeletal changes
  - splenomegaly in childhood; splenic atrophy in adulthood
- SCD-SS often presents with acute pain episode:
  1. aplastic crises
    - ♦ toxins and infections (especially parvovirus B19) transiently suppress bone marrow
  2. splenic sequestration crises
    - ♦ usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
    - ♦ uncommon in adults due to functional asplenia from repeated infarction
  3. vaso-occlusive crises (infarction)
    - ♦ may affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen and extremities), fever, and leukocytosis
    - ♦ precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses and alcohol
  4. acute chest syndrome (see sidebar, H19)
- SCD-SC (most common compound heterozygote)
  - 1:833 live births in African-Americans, common in West Africa
  - milder anemia than HbSS
  - similar complications as HbSS although typically milder and less frequent (exception is proliferative sickle retinopathy, glomerulonephritis and avascular necrosis)
  - spleen not always atrophic in adults

### Investigations

- sickle cell prep (detects sickling of RBCs under the microscope in response to O<sub>2</sub> lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC and other variants

**Table 13. Investigations for Sickle Cell Disease**

	HbAS	HbSS
<b>CBC</b>	Normal	Increased reticulocytes, decreased Hb, decreased Hct
<b>Peripheral blood</b>	Normal; possibly a few target cells	Sickled cells
<b>Hb electrophoresis</b>	HbA fraction of 0.65 (65%) HbS fraction of 0.35 (35%)	No HbA, only HbS and HbF (proportions change with age). Normal amount of HbA2.

### Treatment

- genetic counselling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
- HbSS
  1. folic acid to prevent folate deficiency
  2. hydroxyurea to enhance production of HbF
    - ♦ mechanism of action: stops repression of Hb-gamma chains and/or initiates differentiation of stem cells in which this gene is active
    - ♦ presence of HbF in the SS cells decreases polymerization and precipitation of HbS
    - ♦ NB: hydroxyurea is cytotoxic and may cause bone marrow suppression
  3. treatment of vaso-occlusive crisis
    - ♦ oxygen
    - ♦ hydration (reduces viscosity)
    - ♦ correct acidosis
    - ♦ analgesics/narcotics
    - ♦ indication for exchange transfusion: acute chest syndrome, stroke, multi-organ failure, ICU admission
    - ♦ less routinely: antimicrobials, magnesium (inhibits potassium and water efflux from RBCs thereby preventing dehydration)
  4. prevention of crises
    - ♦ establish diagnosis
    - ♦ avoid conditions that promote sickling (hypoxia, acidosis, dehydration, fever)
    - ♦ vaccination in childhood (pneumococcus, meningococcus, *H. influenzae* b)
    - ♦ prophylactic penicillin (age 3 mo-5 yr)
    - ♦ good hygiene, nutrition and social support
  5. screen for complications
    - ♦ regular bloodwork (CBC, reticulocytes, iron indices, BUN, LFTs, creatinine)
    - ♦ urinalysis annually (proteinuria, glomerulopathy)
    - ♦ transcranial doppler annually until 16 yr old (stroke prevention)
    - ♦ retinal examinations annually from 8 yr old (screen for retinopathy)
    - ♦ echocardiography every two years from 10 yr old (screen for pulmonary hypertension)



#### Organs Affected by Vaso-Occlusive Crisis

Organ	Problem
Brain	Seizures, stroke
Eye	Hemorrhage, blindness
Liver	Infarcts, RUQ syndrome
Lung	Chest syndrome, long-term pulmonary hypertension
Gallbladder	Stones
Heart	Hyperdynamic flow murmurs
Spleen	Enlarged (child); atrophic (adult)
Kidney	Hematuria, loss of renal concentrating ability, proteinuria
Intestines	Acute abdomen
Placenta	Stillbirths
Penis	Priapism
Digits	Dactylitis
Femoral and humeral head	Avascular necrosis
Bone	Infarction, infection
Ankle	Leg ulcers



#### NIH Consensus Development Conference Statement: Hydroxyurea Treatment for Sickle Cell Disease

*Ann Intern Med* 2008;148:932-938

**Efficacy:** Strong evidence for adolescents and adults and there is emerging data supporting its use in children. In the single RCT, the Hb level was higher in hydroxyurea recipients than placebo recipients after 2 yr (difference, 6 g/L), as was HbF (absolute difference, 3.2%). The median number of painful crises was 44% lower than in the placebo arm. The 12 observational studies that enrolled adults reported a relative increase in HbF of 4% to 20% and a relative reduction in crisis rates by 68% to 84%. Hospital admissions declined by 18% to 32%.

**Effectiveness:** Data is limited but seems to be highly effective but is currently underutilized.

**Short-Term harms (within 6 mo):** Dose-related leukopenia, thrombocytopenia, anemia, and decreased reticulocyte count. Others include decreased sperm production and dry skin.

**Long-Term Harms:** Birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug.

## Autoimmune Hemolytic Anemia (AIHA)



**Table 14. Classification of AIHA**

	Warm	Cold
<b>Antibody Allotype</b>	IgG	IgM
<b>Agglutination Temperature</b>	37°C	4-21°C
<b>Direct Coombs' Test (direct anti-globulin test)</b>	Positive for IgG $\pm$ complement	Positive for complement
<b>Etiology</b>	Idiopathic Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin) Secondary to autoimmune disease (e.g. SLE) Drug induced: Type I: hapten-mediated (e.g. penicillin) Type II: immune-complex mediated (e.g. quinine) Type III: "true" anti-RBC Ab (e.g. methylolpa)	Idiopathic Secondary to infection (e.g. mycoplasma pneumonia, EBV) Secondary to lymphoproliferative disorder (e.g. macroglobulinemia, CLL)
<b>Blood Film</b>	Spherocytes	Agglutination
<b>Management</b>	Treat underlying cause Corticosteroids Immunosuppression Splenectomy Folic acid	Treat underlying cause Warm patient Immunosuppression Plasmapheresis Folic acid

## Microangiopathic Hemolytic Anemia (MAHA)

### Definition

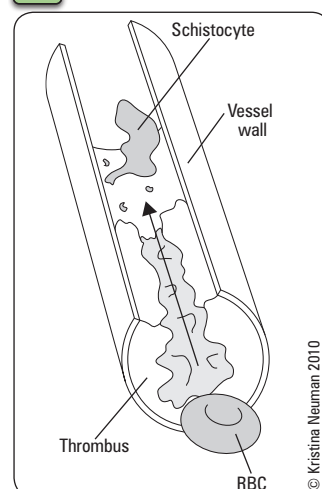
- hemolytic anemia due to intravascular fragmentation of RBCs

### Etiology

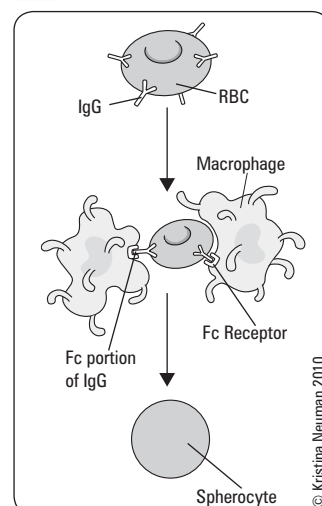
- thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS), see H28
- disseminated intravascular coagulation (DIC), see H30
- eclampsia, HELLP syndrome, AFLP (see [Obstetrics](#), OB17, OB19)
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic antiphospholipid antibody syndrome

### Investigations

- blood film: evidence of hemolysis, schistocytes
- hemolytic work-up
- urine: hemosiderinuria, hemoglobinuria



**Figure 9. Schistocyte**



**Figure 10. Spherocyte**

## Hereditary Spherocytosis

- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
  - spleen makes defective RBCs more spherocytotic (and more fragile) by membrane removal; also acts as site of RBC destruction
- autosomal dominant with variable penetrance

### Investigations

- blood film shows spherocytes, increased osmotic fragility, molecular analysis for spectrin gene

### Treatment

- in severe cases, splenectomy + vaccination against pneumococcus, meningococcus and *H. influenzae* b (avoid in early childhood)

## Hereditary Elliptocytosis

### Definition/Etiology

- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

**Treatment**

- immunizations; splenectomy for severe hemolysis

**G6PD Deficiency****Definition**

- deficiency in glucose-6-phosphate dehydrogenase (G6PD) leads to RBC sensitivity to oxidative stress due to a lack of reduced glutathione (GSH) (Figure 11)

**Pathophysiology**

- X-linked recessive, prevalent in individuals of African, Asian and Mediterranean descent

**Clinical Features**

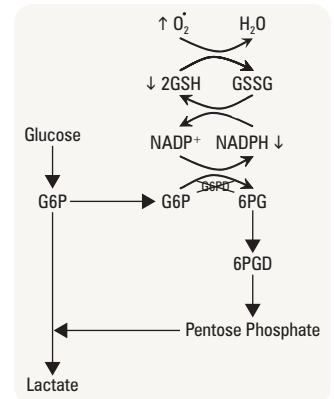
- frequently presents as episodic hemolysis precipitated by:
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

**Investigations**

- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
  - may have features of intravascular hemolysis (e.g. RBC fragments)

**Treatment**

- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases

**Figure 11. G6PD deficiency****Macrocytic Anemia**

- MCV >100 fL
- see Figure 3, *Approach to Anemia*, H5

**Table 15. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia**

	Megaloblastic	Non-Megaloblastic
<b>Morphology</b>	Large, oval, nucleated RBC precursor Hypersegmented neutrophils	Large round RBC Normal neutrophils
<b>Pathophysiology</b>	Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm	Reflects membrane abnormality with abnormal cholesterol metabolism

**Causes of Macrocytic Anemia****ABCDE F**

- A**lcoholism (liver disease)
- B**<sub>12</sub> deficiency
- C**ompensatory reticulocytosis
- D**rugs (cytotoxic, AZT)/Dysplasia
- E**ndocrine (hypothyroidism)
- F**olate deficiency/Fetus (pregnancy)

**Vitamin B<sub>12</sub> Deficiency**

**B<sub>12</sub> (cobalamin)** see [Gastroenterology](#), G17 and [Family Medicine](#) – *Nutrition*, FM5

- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

**Etiology****Table 16. Etiology of Vitamin B<sub>12</sub> Deficiency**

Diet	Gastric	Intestinal Absorption	Genetic
<b>Strict vegan</b> More likely to present in pediatric population	<b>Mucosal atrophy</b> Gastritis, autoimmune	<b>Malabsorption</b> Crohn's, celiac sprue, pancreatic insufficiency	<b>Transcobalamin II deficiency</b>
<b>Vegetarian in pregnancy</b>	<b>Pernicious anemia</b> (see H23) <b>Post-gastrectomy</b>	<b>Stagnant bowel</b> Blind loop, stricture <b>Fish tapeworm</b> <b>Resection of ileum</b> <b>Drugs</b> Neomycin, biguanides, PPI, N <sub>2</sub> O anesthesia	



### Pathophysiology of Pernicious Anemia

- auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize B<sub>12</sub> as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of B<sub>12</sub>
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- female:male = 1.6:1; often >60 yr old

### Clinical Features

- neurological
  - cerebral (common, reversible with B<sub>12</sub> therapy)
    - ♦ confusion, delirium, dementia
  - cranial nerves (rare)
    - ♦ optic atrophy
  - cord (irreversible damage)
    - ♦ subacute combined degeneration
      - posterior columns: decreased vibration sense, proprioception and 2-point discrimination
      - pyramidal tracts: spastic weakness, hyperactive reflexes
  - peripheral neuropathy (variable reversibility)
    - ♦ usually symmetrical, affecting lower limbs more than upper limbs

### Investigations

- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
  - MCV >110 fL
  - low reticulocyte count relative to the degree of anemia (<2%)
- serum B<sub>12</sub> and RBC folate
  - caution: low serum B<sub>12</sub> leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B<sub>12</sub>
  - alternatively, can measure urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils
- bone marrow
  - hypercellularity
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
- bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
- Schilling test (see sidebar) to distinguish pernicious anemia from other causes
  - anti-intrinsic factor antibody, anti-parietal cell antibody

### Treatment

- vitamin B<sub>12</sub> 1000 µg IM monthly for life or 1000-1200 µg PO daily if intestinal absorption intact
- less frequent, higher doses may be as effective (e.g. 1000 µg IM q3mo)
- watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia



#### Characteristics of Megaloblastic Macrocytic Anemia

- Pancytopenia
- Hypersegmented neutrophils
- Megaloblastic bone marrow



#### Schilling Test

##### Part 1

- Tracer dose (1 µg) of radiolabeled B<sub>12</sub>, given PO
- Flushing dose (1 mg) of unlabeled B<sub>12</sub> IM 1 h later to saturate tissue binders of B<sub>12</sub> thus allowing radioactive B<sub>12</sub> to be excreted in urine
- 24 h urine radiolabeled B<sub>12</sub> measured
- Normal >5% excretion (a normal excretion will only be seen if the low B<sub>12</sub> was due to dietary deficiency)

##### Part 2

- Same as part 1, but radiolabeled B<sub>12</sub> given with oral intrinsic factor
- Should be done only if first stage shows reduced excretion
- Normal test result (>5% excretion) = pernicious anemia
- Abnormal test result (<5% excretion) = intestinal causes (malabsorption)



#### Oral Vitamin B<sub>12</sub> versus Intramuscular Vitamin B<sub>12</sub> for Vitamin B<sub>12</sub> Deficiency

*Cochrane DB Syst Rev* 2005;3:CD004655

**Study:** Systematic review. 2 RCTs met inclusion criteria; total 108 patients with follow-up from 90 d to 4 mo.

**Intervention:** One study evaluated 1000 µg of oral B<sub>12</sub> compared to 1000 µg IM B<sub>12</sub> on the same dosing schedule. The other compared 2000 µg daily oral B<sub>12</sub> to 1000 µg IM B<sub>12</sub> on a less frequent dosing schedule. Neurological and hematological end points were evaluated.

**Results:** Meta-analysis was not attempted due to study heterogeneity. Both studies reported improvements in hematological and neurological end-points in both oral and IM groups. No significant difference was observed between groups in either study.

**Conclusions:** Limited data suggesting high dose oral vitamin B<sub>12</sub> (1000-2000 µg) is equivalent to IM vitamin B<sub>12</sub> on the same or less frequent dosing schedule. This data is severely limited by small sample sizes and short follow-up periods. Insufficient numbers of patients with malabsorption conditions were included to generalize these results to the entire primary care population.

## Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables and fortified cereals

### Etiology

Table 17. Etiology of Folate Deficiency

Diet/Deficiency	Malabsorption	Drugs	Increased Demand
Alcoholism	Celiac sprue	Anti-folates (methotrexate)	Pregnancy
Substance abuse	IBD	Anticonvulsants (phenytoin)	Hemolysis
Elderly/Infants	Infiltrative bowel disease	Alcohol	Prematurity
Poor intake	Short bowel syndrome	Oral contraceptive	Exfoliative dermatitis/psoriasis
			Hemodialysis

### Clinical Features

- mild jaundice due to hemolysis of RBCs secondary to ineffective hemoglobin synthesis
- glossitis and angular stomatitis
- melanin pigmentation (rare)
- purpura secondary to thrombocytopenia (rare)
- unlike B<sub>12</sub> deficiency, folate deficiency has no neurologic manifestations

### Investigations

- similar to B<sub>12</sub> deficiency (CBC, reticulocytes, blood film, RBC folate, serum B<sub>12</sub>)
- if decreased RBC folate, rule out B<sub>12</sub> deficiency as cause

### Management

- folic acid 1-5 mg PO OD x 1-4 mo; then 1 mg PO OD maintenance if cause is not reversible



Never give folate alone to an individual with megaloblastic anemia because it will mask B<sub>12</sub> deficiency and neurological degeneration will continue.

## Hemostasis

### Three Phases of Hemostasis

#### 1. Primary Hemostasis

- goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
- vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
- blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 12a)
  - adhesion: platelets adhere to subendothelium via von Willebrand factor (vWF)
  - activation: platelets are activated resulting in change of shape and release of ADP and thromboxane A<sub>2</sub>
  - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

#### 2. Secondary Hemostasis

- platelet plug is reinforced by production of fibrin clot in secondary hemostasis (Figure 12b)
- extrinsic pathway
  - initiation of coagulation *in vivo*
- intrinsic pathway
  - amplification once coagulation has started

#### 3. Fibrin Stabilization and Fibrinolysis (resolution)

- conversion from soluble to insoluble clot
- once healing initiated, clot dissolution (anticoagulant pathway)



Normal hemostasis occurs as a result of the balance between procoagulant and anticoagulant factors.



#### 3 Phases of Hemostasis

- Primary hemostasis
  - Vascular response and platelet plug formation via vWF
- Secondary hemostasis
  - Fibrin clot formation
- Resolution
  - Fibrinolysis

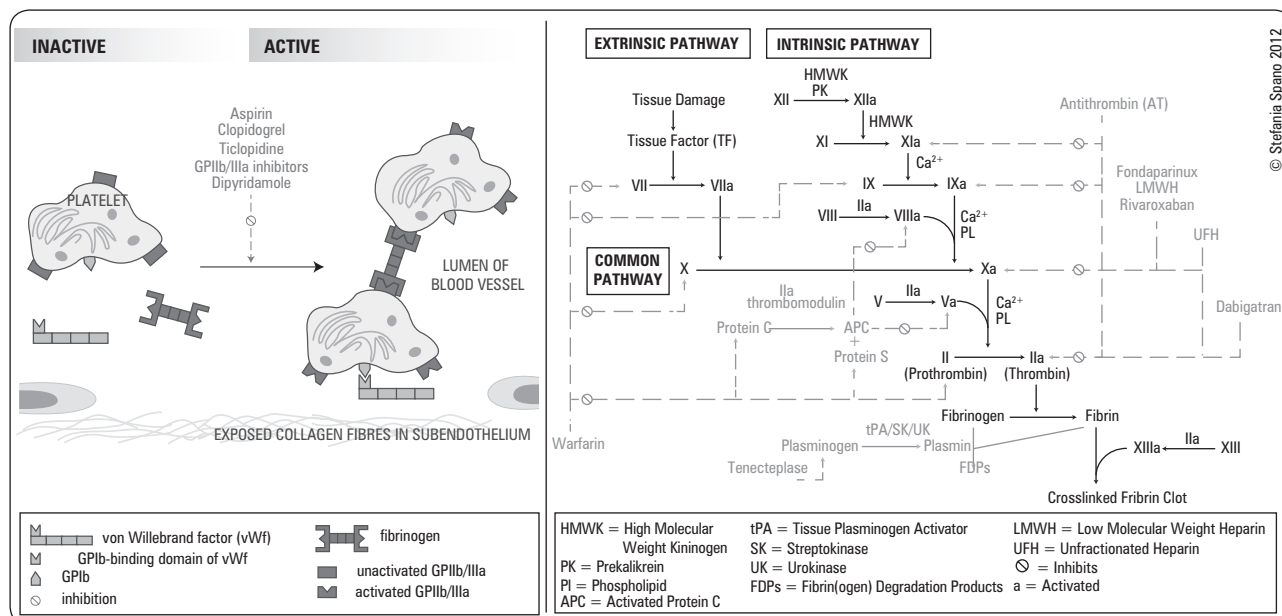


Figure 12a. Platelet activation cascade

Figure 12b. Coagulation cascade

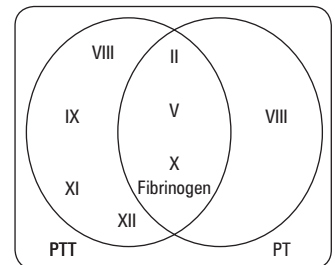
**Table 18. Commonly Used Tests of Hemostasis**

Type of Hemostasis	Test	Reference Range	Purpose	Examples of Associated Diagnoses
<b>Primary</b>	Platelet count	150-400 x 10 <sup>9</sup> /L	To quantitate platelet number	Low in ITP, HUS/TTP, DIC
<b>Secondary</b>	aPTT	22-35 s	Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway Used to monitor heparin therapy and intrinsic pathway factors	Prolonged in hemophilias A and B N.B. High if anti-phospholipid antibodies (i.e. lupus anti-coagulant) are present
	PT	11-24 s	Measures extrinsic pathway (factor VII in particular) and common pathway	Prolonged in factor VII deficiency
	INR	0.9-1.2	Permits determination of extrinsic pathway status independent of laboratory performing measurement Used to monitor warfarin therapy	
	Mixing studies		Differentiate inhibitors of clotting factor(s) from a deficiency in clotting factor(s) Mix patient's plasma with normal plasma in 1:1 ratio and repeat abnormal test	Clotting factor(s) deficiency if test becomes normal Inhibitors of clotting factor(s) if test still abnormal
<b>Fibrinolysis</b>	Euglobulin lysis time	N >90 min	Looks for accelerated fibrinolysis	May be accelerated in DIC or factor XIII deficiency Decreased in hereditary deficiency of fibrinogen
<b>Other</b>	Fibrinogen Fibrinogen degradation products (FDPs), D-dimers Specific factor assays Tests of physiological inhibitors [antithrombin, protein S, protein C, hereditary resistance to activated protein C (APC)] Tests of pathologic inhibitors (e.g. lupus anticoagulant)			

**Tests of Secondary Hemostasis**

PT/INR: Tennis is played outside (Extrinsic pathway)

PTT: Table Tennis is played inside (Intrinsic pathway)

**Figure 13. Clotting factors involved in PT and PTT****Table 19. Signs and Symptoms of Disorders of Hemostasis**

	Primary (Platelet)	Secondary (Coagulation)
<b>Surface Cuts</b>	Excessive, prolonged bleeding	Normal/slightly prolonged bleeding
<b>Onset After Injury</b>	Immediate	Delayed
<b>Site of Bleeding</b>	Superficial i.e. mucosal (nasal, gingival, GI tract, uterine), skin	Deep i.e. joints, muscles, GI tract, GU tract Excessive post-traumatic
<b>Lesions</b>	Petechiae, ecchymoses	Hemarthroses, hematomas

**Table 20. Lab Values in Disorders of Hemostasis**

	PT	PTT	Platelet Count	RBC Count
<b>Hemophilia A/B</b>	N	↑	N	N
<b>vWD</b>	N	±	N/↓	N
<b>DIC</b>	↑	↑	↓	N/↓
<b>Liver Failure</b>	↑	N/↑	N/↓	N
<b>ITP</b>	N	N	↓	N
<b>TTP</b>	N	N	↓	↓

vWD = von Willebrand disease; DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura

## Disorders of Primary Hemostasis

**Definition**

- inability to form an adequate platelet plug due to:
  - disorders of blood vessels
  - disorders of platelets
    - abnormal function
    - abnormal numbers (thrombocytopenia)
  - disorders of vWF

## Classification

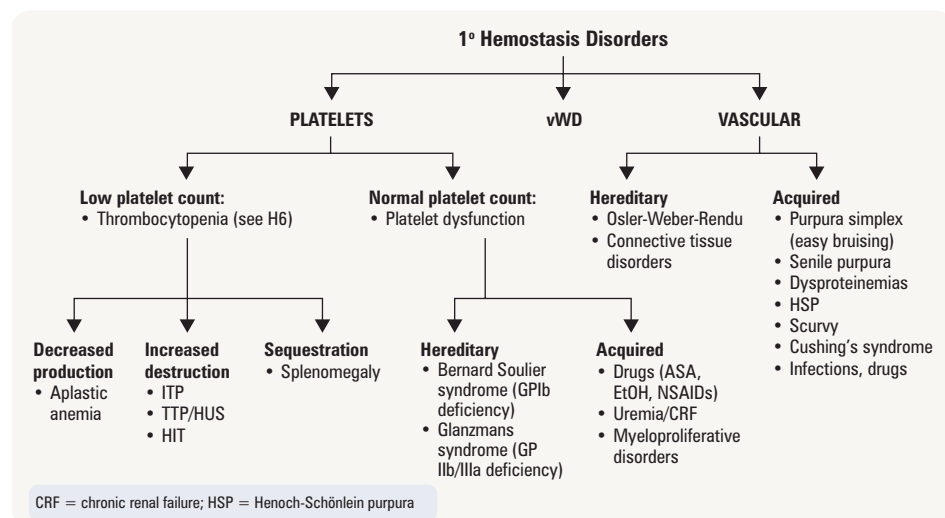


Figure 14. Approach to disorders of primary hemostasis



### Drugs Associated with Thrombocytopenia

TMP-SMX	Heparin	NSAIDs
Vancomycin	Digoxin	Acetaminophen
Rifampin	Amiodarone	Ethanol
Ethambutol	Quinidine	H <sub>2</sub> -antagonists
Amphotericin B	Quinine	



### Mechanisms for HIV-associated Thrombocytopenia

- Direct effect of HIV on marrow
- Immune-mediated platelet destruction
- Some antiretrovirals reduce platelet production



### Should Rituximab be Used Before or After Splenectomy in Patients with Immune Thrombocytopenic Purpura (ITP)?

*Curr Opin Hematol* 2007;14:642-646

**Purpose:** To determine whether the optimal timing for rituximab is before splenectomy, or after failure of splenectomy.

**Results:** Rituximab produces an initial response in approximately 60% of cases, with no significant difference between splenectomized and non-splenectomized patients. Long-term complete responses are observed in 15-20% of cases. Adverse events related to the drug were usually mild or moderate, with a low incidence of infections. Long-term safety data, however, are still lacking. Deaths have been reported for 2.9% of ITP cases treated with rituximab, but they could not be attributed to the study drug.

**Conclusion:** Both the response rate and the response duration appear lower following rituximab than following splenectomy. Although the side effects may be fewer, there is insufficient evidence to support the replacement of splenectomy with rituximab as a second-line treatment of chronic ITP outside a clinical trial. At the present time, the use of immunotherapy before splenectomy can be recommended only in patients at high risk for splenectomy and in those not willing to undergo surgery.

## Immune Thrombocytopenic Purpura (ITP)

Table 21. Immune Thrombocytopenic Purpura

Features	Acute ITP	Chronic ITP
Peak Age	2-6 yr	20-40 yr
Gender	None	F > M (3:1)
History of Recent Infection	Common	Rare
Onset of Bleed	Abrupt	Insidious
Duration	Usually weeks	Months to years
Spontaneous Remissions	80% or more	Uncommon

### ACUTE (CHILD-TYPE) ITP

- see [Pediatrics](#), P49

### CHRONIC (ADULT-TYPE) ITP

- most common cause of isolated thrombocytopenia
- diagnosis of exclusion [i.e. isolated thrombocytopenia (platelets <100 x 10<sup>9</sup>/L) and the absence of any obvious initiating and/or underlying cause]

### Pathophysiology

- an acquired immune-mediated disorder with:
  - anti-platelet antibodies bind to platelet surface → increased splenic destruction and clearance
  - impaired platelet production
  - helper T-cell and cytotoxic T-cell activation also implicated in platelet destruction

### Clinical Presentation

- can present with no symptoms, minimal bruising to a serious bleed (including GI bleed, skin and mucosal hemorrhage or intracranial hemorrhage), lethargy, fatigue

### Investigations

- CBC and reticulocyte count: thrombocytopenia (request retic count if not an isolated thrombocytopenia)
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets (to rule out platelet clumping)
- HIV, HCV (if risk factors are present)
- bone marrow aspirate and biopsy: increased number of megakaryocytes
  - recommended in patients >60 yr of age, pre-splenectomy or have failed multiple lines of ITP treatment, those with systemic symptoms, an abnormal blood film and/or abnormal signs to rule out other causes of thrombocytopenia (e.g. myelodysplasia)

## Treatment

- rarely indicated if platelets  $>30 \times 10^9/L$  unless active bleeding, trauma or surgery

### A. Emergency Treatment (active bleeding (CNS, GI or GU) or in need of emergency surgery)

- general measures: stop drugs reducing platelet function, control blood pressure, minimize trauma
- corticosteroids: prednisone (1 mg/kg) or methylprednisolone (1 g/d x 3 d) or dexamethasone (40 mg PO x 4 d)
- antifibrinolytic: tranexamic acid (1 g PO tid or 1 g IV q6h) if refractory bleeding
- IVIG 1 g/kg/d x 2 doses, or 2 g/kg over 5 d
- platelet transfusion: for life-threatening bleeding
- emergency splenectomy: may be considered, vaccinations prior (pneumococcus, meningococcus, *H. influenzae* b)
- management of intracranial bleeding: IV steroids, IVIG, platelets, emergency splenectomy, and then craniotomy; maintain Plt  $>100$  for at least 7 wk post intracranial hemorrhage

### B. Non-Urgent Treatment (platelet count $<20-30 \times 10^9/L$ and no bleeding OR significant bleeding symptoms with platelet count $<50 \times 10^9$ )

- platelet transfusion does **not** work
- First Line
  - ♦ corticosteroids (dexamethasone 40 mg/d x 4 wk or prednisone 1 mg/kg/d)
  - ♦ IVIG
  - ♦ anti-D: appropriate for Rh+ non-splenectomized patients, but can cause hemolysis (avoid if low Hb at baseline or if DAT is positive)
- Second Line
  - ♦ splenectomy (need vaccinations prior to splenectomy: pneumococcus, meningococcus, *H. influenzae* b)
  - ♦ immunosuppressants (azathioprine, cyclophosphamide)
  - ♦ rituximab
  - ♦ danazol, vincristine
  - ♦ thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag)

## Prognosis

- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- overall relatively benign, mortality 1-2%, (2X higher mortality than the unaffected population)
- major concern is cerebral hemorrhage at Plt  $<5 \times 10^9/L$ , although very rare

## Heparin-Induced Thrombocytopenia (HIT)

- heparin-induced thrombocytopenia: immune mediated reaction following treatment with heparin leading to coagulation activation
- heparin-associated thrombocytopenia: transient thrombocytopenia following administration of heparin

**Table 22. Heparin-Induced Thrombocytopenia (HIT) (Previously Known as HIT Type II)**

<b>Pathophysiology</b>	Immune mediated Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system
<b>Diagnosis</b>	50% reduction in platelets while on heparin within 5-15 wk of initiation
<b>Onset of Decreased Platelets</b>	5-15 wk (if previously exposed to heparin, HIT can develop in hours)
<b>Risk of Thrombosis</b>	~30% (25% of events are arterial)
<b>Clinical Features</b>	Bleeding complications uncommon Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney) Heparin-induced skin necrosis (with LMWH) Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.) Transient global amnesia (rare)
<b>Specific Tests</b>	$^{14}C$ serotonin release assay (uses donor platelets with $^{14}C$ serotonin and heparin with patient's plasma) ELISA for HIT-Ig (more sensitive, less specific than serotonin assay) Ultrasound of lower limb veins for DVT
<b>Management</b>	Clinical suspicion of HIT should prompt discontinuation of heparin (specific tests take several days) Because of 90% cross-reactivity, LMWH should not be substituted Alternative agents include: Argatroban (effective thrombin inhibitor, monitored with aPTT, use with caution in liver disease), fondaparinux (treatment dose, not prophylaxis)



### Evaluation of Pretest Clinical Score (4 Ts) for the Diagnosis of Heparin-induced Thrombocytopenia in Two Clinical Settings

*J Thromb Haemos* 2006;4:759-765

**Study:** Prospective and retrospective clinical score application in two clinical settings (Hamilton General Hospital, HGH; and Greifswald in Germany, GW).

**Population:** 336 patients with suspected HIT.

**Intervention:** Risk stratification with 4Ts clinical score compared with serology for HIT antibody.

**Results:** 1/64 (1.6%) in HGH and 0/55 (0%) in GW with low scores tested positive on HIT serology. 8/28 (28.6%) in HGH and 11/139 (7.9%) in GW with intermediate scores tested positive for HIT. 8/8 (100%) in HGH and 9/42 (21.4%) in GW with high scores tested positive for HIT.

**Conclusions:** A low pretest clinical score can help to rule out HIT in patients with thrombocytopenia.



### Absence of 4 Ts makes HIT unlikely:

Thrombocytopenia  
Timing of platelet count fall  
Thrombosis or other sequelae  
other causes for Thrombocytopenia



LMWH is also associated with HIT, but the risk is less than unfractionated heparin (2.6% in UFH vs. 0.2% in LMWH).



### Heparin-associated thrombocytopenia (previously known as HIT type I)

- Direct heparin mediated platelet aggregation (non-immune)
- Platelets  $>100 \times 10^9/L$
- Self-limited (no thrombotic risk)
- May continue with heparin therapy
- Onset 24-72 h

## Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

Table 23. TTP and HUS

	TTP	HUS
<b>Epidemiology</b>	Predominantly adult	Predominantly children
<b>Etiology</b>	Deficiency of metalloproteinase that breaks down ultra-large vWF multimers <ul style="list-style-type: none"> <li>• Congenital (genetic absence of ADAMTS-13)</li> <li>• Acquired (drugs, malignancy, transplant, HIV-associated, idiopathic)</li> </ul>	Shiga toxin ( <i>E. coli</i> serotype O157:H7)
<b>Clinical features</b>	<ol style="list-style-type: none"> <li>1. Thrombocytopenia</li> <li>2. MAHA</li> <li>3. Neurological symptoms: headache, confusion, focal defects, seizures</li> <li>4. Renal failure</li> <li>5. Fever</li> </ol>	<ol style="list-style-type: none"> <li>1. Severe thrombocytopenia: purpura, epistaxis, hematuria, hemoptysis, GI bleed</li> <li>2. MAHA</li> <li>3. Renal failure: abnormal urinalysis, oliguria, acute renal failure</li> </ol>
<b>Investigations (both TTP, HUS)</b>	CBC and blood film: decreased platelets and schistocytes PT, aPTT, fibrinogen: normal Markers of hemolysis: increased unconjugated bilirubin, increased LDH, decreased haptoglobin Negative Coombs' test Creatinine, urea, to follow renal function Stool C&S (HUS)	
<b>Management (both TTP, HUS)</b>	Medical emergency Plasmapheresis ± steroids Platelet transfusion is contraindicated (increased microvascular thrombosis) Plasma infusion if plasmapheresis is not immediately available TTP mortality ~90% if untreated	



### Pathophysiology of TTP

- vWF secreted by endothelial cells is a very large polymer rapidly cleaved by the ADAMTS-13 protease
- Congenital TTP is due to a deficiency in ADAMTS-13
- Antibodies against ADAMTS-13 are present in acquired TTP



### Differential Diagnosis of TTP:

- Sepsis
- DIC
- HELLP
- Antiphospholipid Ab syndrome
- Evans syndrome (AIHA + ITP)

## Von Willebrand Disease (vWD)

### Pathophysiology

- heterogeneous group of defects
- usually autosomal dominant (type 3 is autosomal recessive)
- qualitative or quantitative abnormality of vWF
  - vWF needed for platelet adhesion and acts as carrier for Factor VIII; abnormality of vWF can affect both primary and secondary hemostasis
  - vWF exists as a series of multimers ranging in size
    - ♦ largest multimers are most active in mediation of platelet adhesion
    - ♦ both large and small multimers complex with Factor VIII
- usually mild in severity

### Classification

- type 1: mild quantitative defect (decreased amount of vWF and proportional decrease in vWF activity) – 75% of cases
- type 2: qualitative defect (vWF activity disproportionately lower than quantity) – 20-25% of cases
- type 3: severe total quantitative defect (no vWF produced) – rare

### Clinical Features

- mild
  - asymptomatic
  - mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia
- moderate to severe
  - as above but more severe, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

### Investigations

Table 24. Investigations in vWD

Test	Expected Result	Test	Expected Result
PTT	N/↑	von Willebrand antigen	↓
Factor VII	N/↓	Blood group	Affects antigen quantification (↓ in group O)
Plt count	N/↓	vWF multimer analysis	Multimer variants
Ristocetin activity	↓ (cofactor for vWF-Plt binding)		



Consider vWD in all women with menorrhagia.



**Treatment**

- desmopressin (DDAVP\*) is treatment of choice for type 1 vWD
  - causes release of vWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs
  - need good response before using with further bleeding
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron®, antifibrinolytic) to stabilize clot formation
- high-purity Factor VIII concentrate containing vWF (Hemate P\*) in select cases and type
  - frozen plasma (FP) is not useful
  - need to monitor vWF and factor VIII levels (very high factor VIII level can cause thrombosis)
- conjugated estrogens (increase vWF levels)

**Prognosis**

- may fluctuate, often improves during pregnancy, inflammation and with age

## Disorders of Secondary Hemostasis

**Definition**

- inability to form an adequate fibrin clot
  - disorders of clotting factors or co-factors
  - disorders of proteins associated with fibrinolysis
- characterized by delayed bleeding, deep muscular bleeding, spontaneous joint bleeding

**Table 25. Classification of Secondary Hemostasis Disorders**

Hereditary	Acquired
Factor VIII: Hemophilia A, vWD	Liver disease
Factor IX: Hemophilia B (Christmas Disease)	DIC
Factor XI	Vitamin K deficiency
Other factor deficiencies are rare	Acquired inhibitors

## Hemophilia A (Factor VIII Deficiency)

**Pathophysiology**

- X-linked recessive, 1/5,000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

**Clinical Features**

- see Table 19 – *Signs and Symptoms of Disorders of Hemostasis*, H25
- older patients may also have HIV or HCV from contaminated blood products

**Investigations**

- prolonged aPTT, normal INR (PT)
- decreased Factor VIII (<40% of normal)
- vWF usually normal or increased

**Treatment**

- desmopressin (DDAVP\*) in mild hemophilia A
- recombinant Factor VIII concentrate for
  - prophylaxis (2-3 times a week at home)
  - minor but not trivial bleeding (e.g. hemarthroses)
  - major potentially life-threatening bleeding (e.g. multiple trauma)
- anti-fibrinolytic agents (e.g. tranexamic acid)

**Hemophilia A****Five Hs**

Hemarthroses  
 Hematomas  
 Hematochezia  
 Hematuria  
 Head hemorrhage

## Hemophilia B (Factor IX Deficiency)

- aka Christmas disease
- X-linked recessive, 1/30,000 males
- clinical and laboratory features identical to hemophilia A (except decreased Factor IX)
- treatment: recombinant Factor IX concentrate, anti-fibrinolytic agents

## Factor XI Deficiency

- aka Rosenthal syndrome
- autosomal recessive; more common in Ashkenazi Jews
- usually mild, often diagnosed in adulthood
- Factor XI level does not correlate with bleeding risk
- treatment: frozen plasma, Factor XI concentrate

## Liver Disease

- see [Gastroenterology](#), G28

### Pathophysiology

- deficient synthesis of all factors except VIII (also made in endothelium and in acute phase response)
- aberrant synthesis of fibrinogen
- deficient clearance of hemostatic 'debris' and fibrinolytic activators
- accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
- miscellaneous: inhibition of secondary hemostasis by FDPs

### Investigations

- peripheral blood film: target cells
- primary hemostasis affected
  - thrombocytopenia 2° to hypersplenism, folate deficiency, alcohol intoxication, DIC, decreased production of thrombopoietin
  - platelet dysfunction (e.g. alcohol abuse)
- secondary hemostasis affected
  - elevated INR (PT), aPTT and TT, low fibrinogen in end-stage liver disease

### Treatment

- supportive, treat liver disease, blood products if active bleeding (frozen plasma, platelets, cryoprecipitate)



#### Investigations in Liver Disease

Factor V, VII, VIII. Expect decreased V and VII because they have the shortest half-life. Factor VIII will be normal or increased because it is produced in the endothelium.

## Vitamin K Deficiency

### Etiology

- drugs
  - oral anticoagulants which inhibit Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease (decreased stores)
- malabsorption (e.g. celiac disease)
- hemorrhagic disease of newborn, see [Pediatrics](#), P71

### Investigations

- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX and X (vitamin K-dependent)

### Treatment

- hold anticoagulant
- vitamin K 1 mg PO for INR between 4.5 and 10 and no active bleeding (excludes hemorrhagic disease of the newborn)
- if bleeding, give vitamin K 10 mg IV
- if life-threatening bleeding and vitamin K antagonist use, give frozen plasma or prothrombin complex concentrate (PCC)
  - PCCs are contraindicated if there is a previous history of HIT
  - use FFP if PCC is contraindicated or unavailable
- note: excessive vitamin K will delay therapeutic warfarin anticoagulation once re-started



#### Vitamin K Dependent Factors

Vitamin K antagonists (e.g. warfarin) affect function of these factors: "1972 Canada vs. Soviets" X, IX, VII, II proteins C and S



PT should improve within 24 h of vitamin K administration (onset is in 6-12 h). If not, search for other causes.

## Disseminated Intravascular Coagulation (DIC)

- see also [Obstetrics](#), OB21

### Definition

- uncontrolled release of plasmin and thrombin leading to intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage

### Etiology

- occurs as a complication of many other conditions
- widespread endothelial damage ± extensive inflammatory cytokine release



#### Factor Levels in Acquired Coagulopathies

Factor	Liver Disease	Vitamin K Def	DIC
V	↓	N	↓
VII	↓	↓	↓
VIII	N/↑	N	↓



DIC is a spectrum which may include thrombosis, bleeding or both.

**Table 26. Etiology of DIC**

Activation of Procoagulant Activity	Endothelial Injury	Reticuloendothelial Injury	Vascular Stasis	Other
Antiphospholipid antibody syndrome (APS) Intravascular hemolysis Incompatible blood, malaria Tissue injury Obstetric complications, trauma, burns, crush injuries Malignancy Solid tumours, hematologic malignancies (especially APLM) Snake venom, fat embolism, heat stroke	Infections/sepsis Vasculitis Metastatic adenocarcinoma Aortic aneurysm Giant hemangioma	Liver disease Splenectomy	Hypotension Hypovolemia Pulmonary embolus	Acute hypoxia/acidosis Extracorporeal circulation

**Clinical Features**

- presence of both hemorrhage and clotting

**Table 27. Clinical Features of DIC**

Signs of Microvascular Thrombosis	Signs of Hemorrhagic Diathesis
<b>Neurological:</b> multifocal infarcts, delirium, coma, seizures <b>Skin:</b> focal ischemia, superficial gangrene <b>Renal:</b> oliguria, azotemia, cortical necrosis <b>Pulmonary:</b> ARDS <b>GI:</b> acute ulceration <b>RBC:</b> microangiopathic hemolysis	Bleeding from any site in the body ( $2^{\circ}$ to decreased platelets and clotting factors) <b>Neurologic:</b> intracranial bleeding <b>Skin:</b> petechiae, ecchymosis, oozing from puncture sites <b>Renal:</b> hematuria <b>Mucosal:</b> gingival oozing, epistaxis, massive bleeding

**Investigations**

- primary hemostasis: decreased platelets
- secondary hemostasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
- fibrinolysis: increased FDPs or D-dimers, short euglobulin lysis time (i.e. accelerated fibrinolysis)
- extent of fibrin deposition: urine output, urea, RBC fragmentation

**Treatment**

- recognize early
- treat underlying disorder
- individualized critical care support
- in hemorrhage: replacement of hemostatic elements with platelet transfusion, frozen plasma, cryoprecipitate
  - maintain platelets  $>50 \times 10^9$  and hemoglobin  $>80$  g/L
  - 4-5 units of FFP if INR  $>1.5$  or aPTT  $>38$
  - 10 units of cryoprecipitate if fibrinogen  $<1$  g/L
  - 1 adult dose of buffy-coat platelets if  $<10 \times 10^9$  ( $<20$  if febrile,  $<50$  before invasive procedure)
- in thrombotic phase: UFH or LMWH in critically ill, non-bleeding patients

**Table 28. Screening Test Abnormalities in Coagulopathies**

Increased INR Only	Increased PTT Only	Both Increased
Warfarin	Hemophilia A and B	Prothrombin deficiency
Vitamin K deficiency	vWD	Fibrinogen deficiency
Factor VII deficiency	Heparin	Factor V and X deficiency
Liver disease	Antiphospholipid Ab	Severe liver disease
Factor VII inhibitors	Factor inhibitors	Factor V and X, prothrombin, and fibrinogen inhibitors
	Factor XI and XII deficiency	Excessive anticoagulation

**Important Etiologies of DIC****OMITS**

Obstetric complications  
Malignancy  
Infection  
Trauma  
Shock



Levels of fibrinogen can still be normal in DIC as it is an acute phase reactant. Serial fibrinogen levels should be measured to see if there is a trending decrease along with an increase in D-dimer.

**Risk of VTE in Hospitalized Patients Receiving Ineffective Antithrombotic Therapy**

Risk Factor	RR (95% CI)	P-value
Age $>75$ yr	1.79 (1.18-2.71)	0.007
Cancer	1.58 (1.01-2.51)	
Previous VTE	1.67 (1.01-2.77)	0.08
Obesity	0.94 (0.59-1.51)	0.91
Hormone therapy	0.51 (0.08-3.38)	0.70
Heart failure	1.08 (0.72-1.62)	0.82
NYHA III	0.89 (0.55-1.43)	0.72
NYHA IV	1.48 (0.84-2.6)	0.27
Acute infectious disease	1.50 (1.00-2.26)	0.06
Acute rheumatic disease	1.45 (0.84-2.50)	0.27

Source: JAMA 2004;164:963-968

**Differential Diagnosis of Elevated D-dimer**

- Arterial thromboembolic disease (MI, CVA, acute limb ischemia, A. fib, intracardiac thrombus)
- Venous thromboembolic disease (DVT, PE)
- DIC
- Preeclampsia and eclampsia
- Abnormal fibrinolysis; use of thrombolytic agents
- Cardiovascular disease, congestive heart failure
- Severe infection/sepsis/inflammation
- Surgery/trauma (tissue ischemia, necrosis)
- Systemic inflammatory response syndrome
- Vasoocclusive episode of sickle cell disease
- Severe liver disease
- Malignancy
- Renal disease (nephrotic syndrome, acute/chronic renal failure)
- Normal pregnancy
- Venous malformation

**Virchow's Triad**

- Endothelial damage
- Stasis
- Hypercoagulability

## Venous Thromboembolism

**Definition**

- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- superficial thrombophlebitis, deep vein thrombosis (DVT) and pulmonary embolism (PE)
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- more common in lower extremity than upper extremity
- incidence  $\sim 1\%$  if age  $>60$  yr
- most important sequelae are pulmonary embolism ( $\sim 50\%$  chance with proximal DVT) and chronic venous insufficiency

### Etiology (Virchow's Triad)

- endothelial damage
  - exposes endothelium to prompt hemostasis
  - leads to decreased inhibition of coagulation and local fibrinolysis
- venous stasis
  - immobilization (post-MI, CHF, stroke, post-op) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see *Hypercoagulable Disorders*, H34)
  - acquired
    - ♦ age (risk increases with age)
    - ♦ surgery (especially orthopedic, thoracic, GI and GU)
    - ♦ trauma (especially fractures of spine, pelvis, femur or tibia, spinal cord injury)
    - ♦ neoplasms (especially lung, pancreas, colon, rectum, kidney and prostate)
    - ♦ blood dyscrasias (myeloproliferative neoplasms, especially PV, ET), PNH, hyperviscosity (multiple myeloma, polycythemia, leukemia, sickle cell disease)
    - ♦ prolonged immobilization (CHF, stroke, MI, leg injury)
    - ♦ hormone related (pregnancy, OCP, HRT, SERMs)
    - ♦ APS
    - ♦ heart failure (risk of DVT greatest with right heart failure and peripheral edema)
- idiopathic (10-20% are later found to have cancer)

### Clinical Features of DVT

- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth and tenderness
- palpable cord (thrombosed vein)
- phlegmasia cerulea dolens and phlegmasia alba dolens with massive thrombosis
- Homan's sign (pain with foot dorsiflexion) is unreliable

### Differential Diagnosis of DVT

- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency, ruptured popliteal cysts, cellulitis, arterial occlusive disease

### Investigations for DVT

- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease and no other acute medical issues/recent surgery
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
  - sensitivity for calf DVT ~70%
- other non-invasive tests include MRI and impedance plethysmography
- venography is the gold standard, but is expensive, invasive and higher risk
- for **Clinical Features** and **Treatment of PE**, see [Respirology](#), R17

## Approach to Treatment of Venous Thromboembolism (VTE)

### Purpose

- prevent further clot extension
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis
- treatment of massive iliofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications, e.g. postphlebitic syndrome, chronic venous insufficiency and chronic thromboembolic pulmonary HTN

### Absolute Contraindications to Treatment

- active bleeding
- severe bleeding diathesis or platelet count  $<20 \times 10^9/L$  ( $<20,000/mm^3$ )
- intracranial bleeding
- neurosurgery or ocular surgery within 10 d

### Relative Contraindications to Treatment

- mild-moderate bleeding diathesis or thrombocytopenia
- brain metastases
- recent major trauma
- major abdominal surgery within the past 2 d
- GI or GU bleeding within 14 d
- endocarditis
- severe hypertension (sBP  $>200$  or dBP  $>120$ )
- recent stroke



#### Wells' Score for VTE

##### Criteria (Score):

- Paralysis, paresis or recent orthopedic casting of lower extremity (1)
- Recently bedridden ( $>3$  d) or major surgery within past 4 wk (1)
- Localized tenderness in deep vein system (1)
- Swelling of entire leg (1)
- Calf swelling  $>3$  cm than other leg (measured 10 cm below the tibial tuberosity) (1)
- Pitting edema greater in the symptomatic leg (1)
- Collateral non varicose superficial veins (1)
- Active cancer or cancer treated within 6 mo (1)
- Alternative diagnosis more **likely** than DVT (e.g. Baker's cyst, cellulitis, muscle damage, superficial venous thrombosis) (-2)

##### Total Score Interpretation:

3-8: High probability, 1-2: Moderate probability, -2-0: Low Probability



#### Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

*NEJM* 2003;349:146-153

**Study:** RCT comparing the efficacy of LMWH (dalteparin) with an oral anti-coagulant agent (coumarin) in preventing recurrent thrombosis in patients with cancer.

**Methods:** Patients with cancer who had acute, symptomatic proximal DVT, PE, or both were randomly assigned to either dalteparin or coumarin treatment for 6 mo.

**Results:** 27 of 336 patients in the dalteparin group had recurrent VTE versus 53 of 336 patients in the coumarin group (hazard ratio, 0.48;  $p=0.002$ ). The probability of recurrent thromboembolism at 6 mo was 9% and 17% in dalteparin and coumarin groups respectively. There was no significant difference in bleeding rates. The mortality rate was 39% in the dalteparin group and 41% in the coumarin group.

**Conclusions:** In patients with cancer and acute VTE, dalteparin was more effective than coumarin in decreasing the risk of recurrent thromboembolism without increasing the risk of bleeding.



#### Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism

*Cochrane DB Syst Rev* 2009;CD001367

**Study:** Meta-analysis of 8 RCTs (2994 patients) comparing different durations of treatment with vitamin K antagonists in patients with symptomatic VTE.

**Results:** In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.18; 95%CI 0.13-0.26). In addition, there was no observed excess of VTE recurrences following cessation of prolonged treatment (i.e. rebound phenomenon) (OR 1.24; 95%CI 0.91-1.69). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61; 95%CI 1.48-4.61).

**Conclusion:** Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.

### Initial Treatment

- low molecular weight heparin (LMWH)
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; <1% HIT; safe and effective outpatient therapy
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis
  - renally cleared – must adjust dose in patients with renal dysfunction
- unfractionated heparin (UFH)
  - in patient with average risk of bleed; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- alternatives to LMWH and UFH
  - heparinoids (patients with HIT), direct thrombin inhibitors (hirudin, lepirudin, argatroban, dabigatran), Factor Xa inhibitors (fondaparinux, rivaroxaban)
  - thrombolytic drugs (e.g. streptokinase, tPA) reserved for acute limb/life-threatening thrombosis, and low bleeding risk

### Long-term Treatment

- warfarin:
  - standard treatment; should be initiated with heparin overlap: dual therapy for at least 5 d, due to initial prothrombotic state, half life of vitamin K factors and risk of warfarin-induced skin necrosis
  - discontinue heparin after INR >2.0 for two consecutive days
  - warfarin should be dosed to maintain INR at 2-3 except in select cases
  - monitor INR twice weekly for 1-2 wk, then weekly until INR stable, then every 2-4 wk
  - LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients (see sidebar, H32)
- duration of anticoagulant treatment (with warfarin unless otherwise noted):
  - first episode DVT with transient risk factor: 3 mo
  - first episode DVT with ongoing risk factor (e.g. cancer, antiphospholipid antibody) or >1 risk factor: consider indefinite therapy
  - first episode DVT with no identifiable risk factor (idiopathic) or single inherited risk factor (e.g. Factor V Leiden): 6-12 mo or indefinite therapy (controversial)
  - recurrent DVT (2 or more episodes): indefinite therapy
- IVC filters
  - temporary filter indicated only if distal acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding)
  - must remove once safe to do so as filter is pro-thrombotic in the longterm (anticoagulation if left in)
- special considerations
  - pregnancy: treat with LMWH during pregnancy, then warfarin for 4-6 wk post-partum (minimum total anticoagulation time of 3-6 mo)
  - surgery: avoid elective surgery in the first month after a venous or arterial thromboembolic event
    - ♦ preoperatively: IV heparin may be used up to 6 h pre-operatively
    - ♦ perioperatively: surgery safe when INR <1.5; warfarin should be discontinued for at least 4 wk pre-operatively to allow INR to fall
    - ♦ postoperatively: IV heparin or LMWH can be used for anticoagulation (start 12 h after major surgery until therapeutic INR reached after restarting warfarin)
    - ♦ for patients at high risk for thromboembolism (VTE <12 wk, recurrent VTE, lupus anticoagulant, atrial fibrillation with prior stroke, mechanical heart valve), IV heparin or LMWH (bridging) should be given before and after the procedure while the INR is below 2.0

### Prophylaxis

- see sidebar
- consider for those with a moderate to high risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), intermittent pneumatic compression (IPC)
- UFH 5000 IU SC bid for moderate risk
- UFH 5000 IU SC tid or LMWH as per hospital protocol (i.e. enoxaparin 40 mg SC daily) or UFH 5000 IU SC tid for high risk

### Contraindications and Adverse Reactions of Anticoagulant Therapy

- absolute: active bleeding, severe bleeding diathesis or platelets <20 x 10<sup>9</sup>/L (<20,000/mm<sup>3</sup>), intracranial bleeding, neuro or ocular surgery within <10 d
- relative: mild-moderate neurologic diathesis or thrombocytopenia, brain metastases, recent major trauma, major abdominal surgery within page 2 d, GI/GU bleed within 14 d, endocarditis, severe HTN (sBP >200 or dBP >120), recent stroke

### Treatment of Pulmonary Embolism (PE)

- see [Respirology](#), R19



#### Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism

*Cochrane DB Syst Rev* 2006;1:CD001367

**Study:** Meta-analysis of 8 RCTs (2994 patients) comparing different durations of treatment with vitamin K antagonists in patients with symptomatic venous thromboembolism (VTE).

**Main Results:** In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.18, CI 0.13-0.26). In addition, there was no observed excess of VTE recurrences following cessation of prolonged vitamin K antagonist therapy (OR 1.24, CI 0.91-1.69). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61, CI 1.48-4.61).

**Conclusion:** Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.



#### Common Medications that Interact with Warfarin

- Acetaminophen (interference with vit K metabolism)
- Allopurinol
- NSAIDs (GI injury)
- Fluconazole
- Metronidazole
- Sulfamethoxazole
- Tamoxifen



#### Initiation of Warfarin Therapy Requires Overlap with Heparin Therapy for 4-5 Days

- 10 mg loading dose of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state.
- Warfarin decreases Factor VII levels in first 48 h INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after approx. 4 d).



#### Low risk surgical patients:

<40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal or thoracic surgery.

#### Moderate risk surgical patients:

>40 yr, >1 risk factor for VTE, GA >30 min.

#### High risk surgical patients:

>40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency or other risk factor.

#### High risk medical patients:

heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD).



# Hypercoagulable Disorders

## Hypercoagulability Workup – Venous Thrombosis

- workup for malignancy or hypercoagulable state indicated for idiopathic VTE in presence of the following: age <50, recurrent VTE, family history of VTE and age <50, unusual site of DVT (portal, hepatic, mesenteric vascular beds), heparin-resistant disease (AT deficiency), warfarin-induced skin necrosis or neonatal purpura fulminans (proteins C or S deficiency). Consider for women with VTE within 12 mo of exposure to OCP
- workup:
  - initial
    - CBC, blood smear, coagulation studies, liver/renal function, urinalysis, fasting homocysteine
    - malignancy work up (see sidebar)
    - anti-phospholipid antibodies (APLA): anticardiolipin antibodies (ACA) and lupus anticoagulant (LA)
    - activated protein C resistance (APCR)
    - DNA: FVL (Factor V Leiden), PT (prothrombin G20210A)
  - post initial insult (>72 h) (as protein levels depleted/consumed by clot)
    - antithrombin (not on heparin)
    - Factor VIII (increased levels predict recurrence)
  - post-treatment
    - proteins C, S (not on warfarin)
- Note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state. Thus more focus is on the reversible/treatable causes (APLA, cancer, etc.)

## CAUSES OF HYPERCOAGULABILITY LEADING TO VENOUS THROMBOEMBOLISM

### Activated Protein C Resistance (Factor V Leiden)

- most common cause of hereditary thrombophilia
- 5% of general population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

### Prothrombin (PT) G20210A

- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

### Protein C and Protein S Deficiency

- protein C inactivates Factor Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous: neonatal purpura fulminans
  - heterozygous:
    - type I: decreased protein C levels
    - type II: decreased protein C activity
  - acquired: liver disease, sepsis, DIC, warfarin
  - 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, warfarin

### Antithrombin Deficiency

- antithrombin slowly inactivates thrombin in the absence of heparin, rapidly inactivates thrombin in the presence of heparin
- autosomal dominant inheritance or urinary losses in nephrotic syndrome
  - type I: decreased AT levels
  - type II: decreased AT activity
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to unfractionated heparin (LMWH must be used)

### Elevated Factor VIII Levels

- an independent marker of increased thrombotic risk
- genetic basis for increased levels poorly understood

### Disorders of Fibrinolysis

- include congenital plasminogen deficiency, tissue plasminogen activator deficiency

### Antiphospholipid Antibody Syndrome (APS)

- definition:  $\geq 1$  clinical and  $\geq 1$  laboratory criteria
  - clinical: thrombosis, spontaneous abortions, fetal loss, premature birth before 34 wk
  - laboratory: anticardiolipin or lupus anticoagulant antibodies
- mechanism: not well understood, antibodies interact with platelet membrane phospholipid causing increased adhesion and aggregation; can also interfere with action of proteins C and S
- see [Rheumatology](#), RH12



#### Common Causes of Hypercoagulability

##### CALM APES

Protein **C** deficiency  
 Antiphospholipid **Ab**  
 Factor **V** Leiden  
 Malignancy  
 Antithrombin deficiency  
 Prothrombin G20210A  
 Increased Factor **VIII** (Eight)  
 Protein **S** deficiency



Although lupus anti-coagulant prolongs PTT, its main clinical feature is thrombosis.



Protein C, protein S, and ATIII are decreased during acute thrombosis – therefore to test for deficiency, must be tested outside of this time period.



#### Causes of Both Venous and Arterial Thrombosis include:

- Antiphospholipid antibodies
- Myeloproliferative neoplasms
- Heparin induced thrombocytopenia
- Distal venous clot with patent foramen ovale



Malignancy is a common cause of acquired hypercoagulability.

#### Workup may include (controversial):

- Complete history and physical
- Routine bloodwork
- Urinalysis
- CXR and abdominal ultrasound
- Age appropriate screening: mammogram, Pap, PSA, colonoscopy
- Close follow-up





# Hematologic Malignancies and Related Disorders

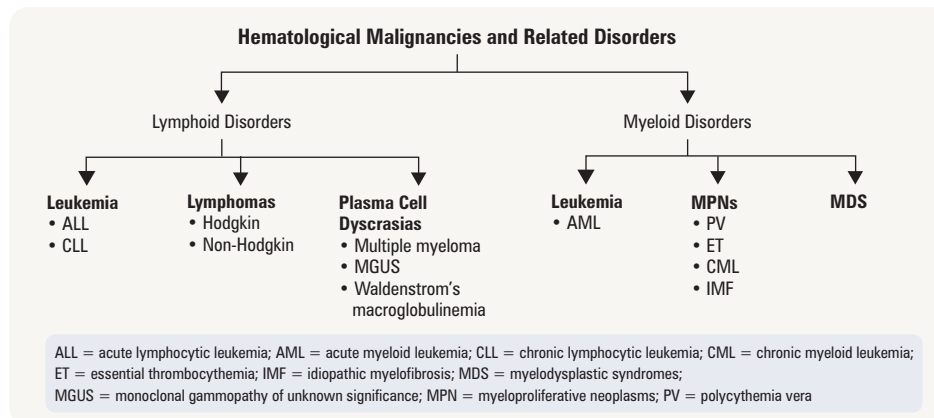


Figure 15. Overview of hematologic malignancies and related disorders

## Myeloid Malignancies

### Acute Myeloid Leukemia (AML)

#### Definition

- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

#### Epidemiology

- incidence increases with age; median age of onset is 65 yr old
- accounts for 10-15% of childhood leukemias

#### Risk Factors

- myelodysplastic syndromes (MDS), benzene, radiation, alkylating agents as treatment for previous malignancy

#### Pathophysiology

- etiology subdivided into:
  - primary: *de novo*
  - secondary: hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to:
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; tumour lysis syndrome

#### Clinical Features

- anemia, thrombocytopenia (associated with DIC in PML), neutropenia (even with normal WBC), leads to infections, fever
- thrombocytopenia (associated with DIC in promyelocytic leukemia)
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - hepatosplenomegaly (in ALL)
  - lymphadenopathy (not marked)
  - skin: leukemia cutis
  - gonads (in ALL)
  - eyes: Roth spots, cotton wool spots, vision changes (uncommon)
- leukostasis/hyperleukosis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, priapism



#### Typical Age of Presentation of Leukemias

- ALL: Children and older adults
- CML: 40-60 yr
- AML, CLL: >60 yr



**Leukemia:** malignant cells arise in bone marrow and may spread elsewhere (including blood, lymph nodes and lymphoid tissue).

**Lymphoma:** malignant cells arise in lymph nodes and lymphoid tissues and may spread elsewhere (including blood and bone marrow).

**BUT** the location where the malignant cells are found does not solely define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes).



#### Acute Leukemia

**Definition (WHO):** presence of 20% blast cells or greater in bone marrow at presentation.

**Classification:** divided into myeloid (AML) and lymphoid (ALL) depending on whether blasts are myeloblasts or lymphoblasts, respectively.



Auer rods are pathognomonic for AML.



#### 2008 WHO Classification of AML and Related Neoplasms

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Myeloid sarcoma
- Myeloid proliferations related to Down Syndrome
- Blastic plasmacytoid dendritic cell neoplasm
- AML, not otherwise specified (equivalent FAB classification)
  - Undifferentiated (M1)
  - Myeloblastic (M2)
  - Promyelocytic (M3)
  - Myelomonocytic (M4)
  - Monocytic (M5)
  - Erythroleukemic (M6)
  - Megakaryocytic (M7)
  - Acute basophilic leukemia
  - Acute panmyelosis with myelofibrosis

- metabolic effects; aggravated by treatment (rare)
  - increased uric acid → nephropathy, gout
  - release of phosphate → decreased  $\text{Ca}^{2+}$ , decreased  $\text{Mg}^{2+}$
  - release of procoagulants → DIC (higher risk in acute promyelocytic leukemia)
- decreased or normal  $\text{K}^+$  before treatment, increased  $\text{K}^+$  after treatment

### Investigations

- bloodwork:
  - CBC: anemia, thrombocytopenia, variable WBC
  - INR, aPTT, fibrin degradation products (FDP), fibrinogen (in case of DIC)
  - increased LDH, increased uric acid, increased  $\text{PO}_4^{3-}$  (released by leukemic blasts), decreased  $\text{Ca}^{2+}$
  - baseline renal and liver function tests
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- bone marrow aspirate:
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytochemical and/or immunotypic features are used to establish lineage and maturation (see sidebar for WHO classification of AML, H35)
- CXR to r/o pneumonia, ECG, MUGA scan prior to chemotherapy (cardiotoxic)

### Treatment

- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
  - all AML subtypes treated similarly except promyelocytic variant with t(15:17) translocation
    - ♦ all-trans-retinoic acid (ATRA) added to induce differentiation
- treatment strategy:
  1. **Induction:** chemotherapy to induce complete remission of AML (see sidebar)
    - ♦ several possible regimens [e.g. cytarabine with anthracycline (daunorubicin)]
    - ♦ patients with poor response to initial induction therapy – worse prognosis
    - ♦ must ensure reversal of DIC, platelet transfusions if <10
  2. **Consolidation:** to prevent recurrence
    - ♦ intensive consolidation chemotherapy
    - ♦ stem cell transplantation – autologous or allogeneic (younger patients with better performance status)
- consider acceleration with hematopoietic growth factors (e.g. G-CSF) if severe infection develops
- supportive care
  - screening for infection via regular C&S of urine, stool, sputum, oropharynx, catheter sites, perianal area
  - fever: C&S of all orifices, CXR, start antibiotics
  - platelet and RBC transfusions (irradiated to prevent transfusion-related GVHD) ± EPO
  - prevention and treatment of metabolic abnormalities
    - ♦ allopurinol for prevention of hyperuricemia

### Prognosis

- achievement of first remission
  - 70-80% if ≤60 yr old, 50% if >60 yr old
  - median survival 12-24 mo
  - 5 yr survival 40%
  - prognosis related to cytogenetics (favourable, intermediate or adverse)



**Cure:** survival that parallels age-matched population.

**Complete Remission:** tumour load below threshold of detectable disease (normal peripheral blood film, normal bone marrow with <5% blasts, normal clinical state).



#### 2008 WHO MDS Classification

- Refractory cytopenia with unilineage dysplasia
- Refractory anemia
- Refractory neutropenia
- Refractory thrombocytopenia
- Refractory anemia with ringed sideroblasts (RAS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)
- Refractory anemia with excess blasts (RAEB)
- Myelodysplastic syndrome with isolated del (5q)
- Myelodysplasia unclassified (seen in cases of megakaryocyte dysplasia with fibrosis and others)
- Childhood myelodysplastic syndrome



MDS is a cause of macrocytic anemia.



**Myelodysplastic Syndromes:** ineffective maturation

**Myeloproliferative Neoplasms:** overproduction of mature cells

## Myelodysplastic Syndromes (MDS)

### Definition

- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias
- syndromes defined according to World Health Organization (WHO) classifications (see sidebar)

### Pathophysiology

- disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular)
- intramedullary apoptosis: programmed cell death within bone marrow
  - both processes lead to reduced mature cells in periphery
- <30% develop AML

### Risk Factors

- elderly, post-chemotherapy, benzene or radiation exposure
- occurs in 60/100,000 in patients >60 yr old

### Clinical Features

- insidious onset: associated with those of pancytopenia
- infections and bleeding out of proportion with peripheral blood counts

## Investigations

- diagnosed by:
  - anemia  $\pm$  thrombocytopenia  $\pm$  neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bilobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size and cytoplasm (e.g. giant hypogranular platelets)
- bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
  - bone marrow: dysplastic and often normocellular/hypercellular
  - cytogenetics: partial or total loss of chromosomes 5, 7, Y, or trisomy 8

## Prognosis

- Revised International Prognostic Scoring System (IPSS-R) uses 5 factors to estimate mean survival:
  - cytology, % bone marrow blasts, hemoglobin, platelets, absolute neutrophil count
  - based on the calculated score, a patient's MDS prognostic risk is "Very Low", "Low", "Intermediate", "High" or "Very High" with a mean survival of 8.7, 5.3, 3.0, 1.6 and 0.8 yr, respectively

## Treatment

- low risk** of transformation to acute leukemia (IPSS-R Very Low or Low)
  - erythropoietin stimulating agents weekly is first line in reducing transfusion requirements
  - 5q(-) cytogenetic: Revlimid<sup>®</sup> PO
  - supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- high risk** of transformation to acute leukemia (IPSS-R Intermediate, High or Very High)
  - supportive care
  - stem cell transplantation if age <65 yr
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-Azacytidine), histone deacetylase inhibitors



### Use of Epoetin and Darbepoetin in Patients with Cancer

*Blood* 2008;111:25-41

Clinical practice guideline update by American Societies of Hematology and Clinical Oncology (2007)

#### Initial Recommendations:

- Initiate an erythropoiesis-stimulating agent (ESA) when hemoglobin (Hb) is 100 g/L (10 g/dL) in patients with palliative chemotherapy-associated anemia to decrease the need for transfusions.
- Discontinue ESAs when patient not responding to treatment beyond 6-8 wk.
- Monitor iron stores and supplement iron intake for ESA-treated patients when necessary.
- Use ESAs cautiously with chemotherapy or in patients with an elevated risk for thromboembolic complications.
- It is not recommended that ESA be used for therapy in patients with cancer who are not receiving chemotherapy, as it increases thromboembolic risks and lowers survival rate. Patients with low-risk myelodysplasia are an exception.

# Myeloproliferative Neoplasms (MPNs)

## Definition

- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets and other cells of myeloid lineage)

## Epidemiology

- mainly middle-aged and older patients (peak 60-80 yr)

## Prognosis

- may develop marrow fibrosis with time
- all disorders may progress to AML

**Table 29. Chronic Myeloproliferative Disorders**

	CML	PV	IMF	ET
Hct	↓/N	↑↑	↓	N
WBC	↑↑	↑	↑/↓	N
Plt	↑/↓	↑	↑/↓	↑↑↑
Marrow fibrosis	±	±	+++	±
Splenomegaly	+++	+	+++	+
Hepatomegaly	+	+	++	-
Genetic Association	<i>bcr-abl</i> mut. (90+%)	JAK2 mut. (95%)	JAK2 mut. (~50%)	JAK2 mut. (~50%)

PV = polycythemia vera; CML = chronic myeloid leukemia; MF = idiopathic myelofibrosis; ET = essential thrombocythemia



Basophilia is uncommon in other medical conditions.

## Chronic Myeloid Leukemia (CML)



### Definition

- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

### Epidemiology

- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

### Pathophysiology

- Philadelphia chromosome (Ph)
  - translocation between chromosomes 9 and 22
  - the *c-abl* proto-oncogene is translocated from chromosome 9 to "breakpoint cluster region" (bcr) of chromosome 22 to produce *bcr-abl* fusion gene, an active tyrosine kinase



Detection of the *bcr-abl* fusion gene is a diagnostic test for CML (present in over 90% of patients).

### Clinical Features

- 3 clinical phases**
  - chronic phase:** 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - accelerated phase:** impaired neutrophil differentiation
    - circulating blasts (10-19%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytopenia  $<100 \times 10^9/L$
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
  - blast crisis:** more aggressive course, blasts fail to differentiate
    - blasts (>20%) in peripheral blood or bone marrow; reflective of acute leukemia (1/3 ALL, 2/3 AML)
- clinical presentation
  - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
  - nonspecific symptoms
    - fatigue, weight loss, malaise, excessive sweating, fever
  - secondary to splenic involvement
    - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
    - splenomegaly (most common physical finding)
  - anemia
  - bleeding: secondary to platelet dysfunction
  - pruritus, PUD: secondary to increased blood histamine
  - leukostasis, priapism, encephalopathy (rare): secondary to very elevated WBC (rare)

### Investigations

- high increase in WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
  - WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
- peripheral blood film
  - leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  - presence of different mid-stage progenitor cells differentiates it from AML
- bone marrow
  - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
- molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
- abdominal imaging for spleen size

### Treatment

- symptomatic:**
  - allopurinol and antihistamines
- chronic phase:**
  - imatinib mesylate (Gleevec®): inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for *bcr-abl*
    - if loss of response or intolerance (~25%), trial of 2nd (dasatinib) or 3rd (nilotinib) generation inhibitors
  - interferon- $\alpha$ : may improve response to tyrosine kinase inhibitors
  - hydroxyurea in palliative setting
  - bone marrow transplantation if progression to accelerated or blast phases: CML (curative)
- accelerated phase or blast phase:**
  - refer for clinical trial or 2nd/3rd generation TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard AML induction
- stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones



**Chronic Myeloproliferative Neoplasias: Six-year follow-up of patients receiving imatinib for the first-line treatment of CML**

*Leukemia* 2009;23:1054-1061

The Randomized Study of Interferon vs. ST1571 (IRIS) trial enrolled patients with chronic phase chronic myeloid leukemia (CML-CP) to either imatinib (n=533) or interferon- $\alpha$  (IFN) plus cytarabine (n=553). Assessing the imatinib arm specifically at the sixth year point, there were no reports of disease progression to accelerated phase (AP) or blast crisis (BC), toxicity profile was unchanged, and cytogenetic response rate was 82%. Estimated event-free survival was 83% and rate of freedom from progression to AP and BC was 93%. This 6-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.

- treatment success is monitored based on therapeutic milestones:
  - hematologic: improved WBC and platelet counts, reduced basophils
  - cytogenetic: undetectable Philadelphia-chromosome in the bone marrow
  - molecular: reduction/absence of *bcr-abl* transcripts in periphery and marrow

### Prognosis

- survival dependent on response
  - those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  - those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
- acute phase (blast crisis – usually within 3-5 yr)
  - 2/3 develop a picture similar to AML
    - ♦ unresponsive to remission induction
  - 1/3 develop a picture similar to ALL
    - ♦ remission induction (return to chronic phase) achievable

## Polycythemia Vera (PV)

### Definition

- stem cell disorder characterized by elevated RBC mass (erythrocytosis) ± increased white cell and platelet production

### Clinical Features

- symptoms are secondary to high red cell mass and hyperviscosity (see *Erythrocytosis*, H6)
- bleeding complications: epistaxis, gingival bleeding, ecchymoses and GI bleeding
  - due to platelet abnormalities
- thrombotic complications: DVT, PE, thrombophlebitis, increased incidence of stroke, MI
  - due to increased blood viscosity, increased platelet number and/or activity
- erythromelalgia (burning pain in hands and feet and erythema of the skin)
  - associated with platelets >400 x 10<sup>9</sup>/L
  - pathognomonic microvascular thrombotic complication in PV and ET
- pruritus, especially after warm bath or shower (40%)
  - due to cutaneous mast cell degranulation and histamine release
- epigastric distress, PUD
  - due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity
- gout (hyperuricemia)
  - due to increased cell turnover
- characteristic physical findings
  - plethora (ruddy complexion) of face (70%), palms
  - splenomegaly (70%), hepatomegaly (40%)

### Investigations

- see *Erythrocytosis*, H6
- must rule out secondary polycythemia
- diagnosis (WHO 2008) requires either both major criteria plus one minor criteria OR the first major criterion plus 2 minor criteria:
  - Major Criteria:
    1. hemoglobin >18.5 g/dL in men, 16.5 g/dL in women or other evidence of increase red cell volume
    2. presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation
  - Minor Criteria:
    1. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation
    2. serum erythropoietin level below the reference range for normal
    3. endogenous erythroid colony formation in vitro

### Treatment

- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- low-dose Aspirin® (for antithrombotic prophylaxis, will also treat erythromelalgia)
- allopurinol: as needed
- antihistamines: as needed

### Prognosis

- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)



Erythromelalgia is a pathognomonic microvascular thrombotic complication in PV and ET.



#### Efficacy and Safety of Low-dose Aspirin® in Polycythemia Vera

*N Engl J Med* 2004;350:114-124

**Study:** Double-blind, placebo-controlled, RCT.

**Participants:** 518 patients with polycythemia vera (PV) with no clear indication for, or contraindication to, ASA therapy.

**Intervention:** Patients received either low-dose ASA 100 mg daily (n=253) or placebo (n=265) and were followed for up to 5 yr.

**Primary Outcome:** Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus PE and major venous thrombosis.

**Results:** Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41; p=0.09 and RR 0.4; p=0.03, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.

**Conclusion:** Low-dose ASA can safely prevent thrombotic complications in patients with PV.



#### Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

*NEJM* 2013;368:22-33

**Study:** Prospective, RCT, mean follow-up of 28.9 mo. Blinding not described.

**Population:** 365 patients with JAK2-positive polycythemia vera being treated with phlebotomy, hydroxyurea or both.

**Intervention:** Patients were randomized to a target hematocrit <45% (low-hematocrit group) or 45-50% (high-hematocrit group).

**Outcome:** Composite of time until death from cardiovascular causes of major thrombotic events.

**Results:** The hazard ratio (HR) for the primary outcome was 3.91 (95% CI, 1.45-10.53, P=0.007), while the HR for the primary outcome plus superficial venous thrombosis was 2.69 (95% CI, 1.19-6.12, P=0.02) for the high-hematocrit vs. low-hematocrit group.

**Conclusions:** The hematocrit target of <45% was associated with a lower incidence of CV death, major thrombotic events and superficial venous thrombosis in patients with polycythemia vera.



## Idiopathic Myelofibrosis (IMF)



### Definition

- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

### Epidemiology

- rare, median age at presentation is 65 yr

### Pathophysiology

- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (primitive RBCs and WBCs present in blood)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

### Clinical Features

- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

### Investigations

- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B<sub>12</sub> (2° to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets and megakaryocyte fragments
- JAK2 PCR
- bone marrow aspirate: “dry tap” in as many as 50% of patients (no blood cells aspirated)
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

### Treatment

- allogeneic stem cell transplant is potentially curative
- symptomatic treatment:
  - transfusion for anemia
  - erythropoietin: 30-50% of patients respond
  - androgens (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, systemic symptoms
    - ♦ α-interferon (as second line therapy)
    - ♦ splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis, symptomatic splenomegaly
  - thalidomide, JAK2 inhibitors, and etanercept may improve quality of life and spleen size, but not survival

### Prognosis

- International Prognostic Scoring System (IPSS) for IMF uses 5 factors to determine mean survival:
  - presence of constitutional symptoms; age >65; hemoglobin <100 g/L; leukocyte count >25,000/mm<sup>3</sup>; circulating blast cells ≥1%
  - based on the calculated score, a patient's IMF is categorized as “low”, “intermediate 1”, “intermediate 2”, or “high” with a mean survival of 135, 95, 48 and 27 mo respectively
- risk of transformation to AML (8-10%)



Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PV or ET.



A “leukoerythroblastic” blood film (RBC and granulocyte precursors) implies bone marrow infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF).



IMF typically has a dry BM aspirate and teardrop RBCs (aspiration gives no blood cells).



#### A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis

*N Engl J Med* 2012;366:799-807

**Study:** Double-blinded RCT of 309 patients with myelofibrosis randomized to ruxolitinib or placebo.

**Outcome:** Primary outcome was reduction in spleen volume of >35% at 24 wk. Secondary outcomes were durability of response, symptom burden, and overall survival.

**Results:** A greater proportion of patients on ruxolitinib had reduction in spleen volume >35% (41.9% vs. 0.7%) and this was sustained in 67% at 48 wk. Ruxolitinib also led to greater symptom improvement (45% vs. 5.3%) and less mortality (13 vs. 24). There was no difference in rate of discontinuation due to adverse events (11.0% vs. 10.6%) but anemia and thrombocytopenia were more common with ruxolitinib.

**Conclusions:** Ruxolitinib reduced spleen size, improved symptoms, and improved overall survival, compared with placebo.

## Essential Thrombocythemia (ET)

### Definition

- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocythemia



## Epidemiology

- increases with age; F:M = 2:1, but F=M at older age

**Diagnosis** (2008 WHO Criteria) requires meeting all four criteria:

- sustained platelet count  $>450 \times 10^9/L$
- bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes. No significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
- not meeting WHO criteria for PV, primary myelofibrosis, BCR-ABL CML or myelodysplastic syndrome or other myeloid neoplasms
- demonstration of JAK2 V617F (or in its absence another clonal marker), no evidence for reactive thrombocytosis

## Clinical Features

- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation  $\rightarrow$  microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI; associated with platelets  $>1000 \times 10^9/L$ )
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

## Investigations

- CBC: increased platelets; may have abnormal platelet aggregation studies
- JAK2 PCR assay
- bone marrow hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased  $K^+$ , increased  $PO_4^{3-}$  ( $2^\circ$  to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

## Treatment

- low dose ASA if previous history of thrombotic event,  $\geq 1$  cardiovascular risk factors, older or symptomatic
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st line therapy), anagrelide, interferon- $\alpha$ , or  $^{32}P$  (age  $>80$  or lifespan  $<10$  yr)
- splenectomy not recommended (increased risk of bleeding episodes, thrombosis)



### Etiology of Secondary Thrombocythemia

- Infection
- Inflammation (IBD, arthritis)
- Malignancy
- Hemorrhage
- Iron deficiency
- Hemolytic anemia
- Post splenectomy
- Post chemotherapy



### Anagrelide vs. Hydroxyurea for Essential Thrombocythemia: ANAHYDRET Study, a Randomized Controlled Trial

Blood 2013;121:1720-8

**Study:** Prospective, non-inferiority, RCT. Majority of patients followed beyond 1 yr.

**Population:** 259 previously untreated, high-risk patients with essential thrombosis as per the WHO guidelines.

**Intervention:** Patients were randomized to receive either non-immediate release formulation of anagrelide or hydroxyurea.

**Outcome:** Examined platelet counts, hemoglobin levels, leukocyte counts, and occurrence of ET-related events.

**Results:** The hazard ratio (HR) of developing thrombocythemia was 1.19 (95% CI, 0.61-2.30). The HR for a reduction of hemoglobin was 1.03 (95% CI, 0.57-1.81), and 0.92 (95% CI, 0.57-1.46) for leukocytosis. There was no statistical difference in occurrence of major or minor arterial or venous thrombosis, severe or minor bleeding events, or rate of discontinuation between the two arms.

**Conclusions:** In patients with ET, anagrelide is non-inferior to hydroxyurea in the prevention of thrombotic complications.



There is an asymptomatic "benign" form of essential thrombocythemia with a stable or slowly rising platelet count. Treatment includes observation, ASA, sulfapyrazone or dipyridamole.



75% of ALL occurs in children  $<6$  yr old; second peak at age 40.

# Lymphoid Malignancies

## Acute Lymphoblastic Leukemia (ALL)

### Definition

- malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
  - B-cell: precursor B lymphoblastic leukemia
  - T-cell: precursor T lymphoblastic leukemia
- The French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged, as morphology is not prognostic

### Clinical Features

- see *Acute Myeloid Leukemia*, H35 for full list of symptoms
- distinguish ALL from AML based on Table 30
- clinical symptoms usually secondary to:
  - bone marrow failure:** anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), thrombocytopenia
  - organ infiltration:** tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

### Investigations

- CBC: increased leukocytes  $>10 \times 10^9/L$  (occurs in 50% of patients); neutropenia, anemia or thrombocytopenia
- may have increased uric acid,  $K^+$ ,  $PO_4^{3-}$ ,  $Ca^{2+}$ , LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- cytogenetics: Philadelphia (Ph) chromosome in  $\sim 25\%$  of adult ALL cases

- CXR: patients with ALL may have a mediastinal mass
- LP prior to systemic chemotherapy to assess for CNS involvement (ensure adequate platelet count and PT/PTT)

### Treatment

- eliminate abnormal cloned cells:
  1. **Induction:** to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
  2. **Consolidation and/or intensification chemotherapy**
    - consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
    - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. **Maintenance chemotherapy:** low dose intermittent chemotherapy over prolonged period (2-3 yr) to prevent relapse
  4. **Prophylaxis:** CNS radiation therapy or methotrexate (intrathecal or systemic)
- hematopoietic stem cell transplantation: potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

### Prognosis

- depends on response to initial induction or if remission is achieved following relapse
- good prognostic factors: young, WBC  $<30 \times 10^9/L$ , T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 80% long term remission ( $>5$  yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of *bcr-abl* fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5-yr survival

**Table 30. Differentiating AML From ALL**

AML	ALL
Big people (adults)	Small people (kids)
Big blasts	Small blasts
Big mortality rate	Small mortality rate (kids)
Lots of cytoplasm	Less cytoplasm
Lots of nucleoli (3-5)	Few nucleoli (1-3)
Lots of granules and Auer rods	No granules
Myeloperoxidase, Sudan black stain	PAS (periodic acid-Schiff)
Maturation defect beyond myeloblast or promyelocyte	Maturation defect beyond lymphoblast



#### Treatment of ALL vs. AML

- No proven benefit of maintenance chemotherapy in AML
- No routine CNS prophylaxis in AML



**To Differentiate AML From ALL:**  
Remember **Big** and **SmALL**  
(see Table 30)

## Lymphomas

### Definition

- collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease and constitutional symptoms

**Table 31. Ann Arbor System for Staging Lymphomas**

Stage	Description
I	Involvement of a single lymph node region or extralymphatic organ or site
II	Involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm; may or may not be accompanied by single extra lymphatic site or splenic involvement
IV	Diffuse involvement of one or more extralymphatic organs including bone marrow

- subtypes:
  - A = absence of B-symptoms (see *Approach to Lymphadenopathy*, H11)
  - B = presence of B-symptoms



- Ann Arbor staging can be used for both Hodgkin and non-Hodgkin lymphoma, but grade/histology is more important for non-Hodgkin lymphoma because the outcome differs significantly depending on type of lymphoma.
- Prognostic scores are different for indolent versus aggressive lymphomas.
- Highly aggressive lymphomas act like acute leukemias.



Hodgkin is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells.

**Table 32. Chromosome Translocations**

Translocation	Gene Activation	Associated Neoplasm
t(8;14)	c-myc activation	Burkitt's lymphoma
t(14;18)	bcl-2 activation	Follicular lymphoma
t(9;22)	Philadelphia chromosome ( <i>bcr-abl</i> hybrid)	CML, ALL in adults (25% of the time)
t(11;14)	Overexpression of cyclin D1 protein	Mantle cell lymphoma

## Hodgkin Lymphoma



### Definition

- malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal centre B-cells)

### Epidemiology

- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases, causal role not determined

### Clinical Features

- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
- splenomegaly (50%) ± hepatomegaly
- mediastinal mass
  - found on routine CXR, may be symptomatic (cough)
  - rarely may present with SVC syndrome, pleural effusion
- systemic symptoms
  - B symptoms (especially in widespread disease; fever in 30%), pruritus
- non-specific/paraneoplastic
  - alcohol-induced pain in nodes, nephrotic syndrome
- starts at a single site in lymphatic system (node), spreads first to adjacent nodes
  - disease progresses in contiguity with lymphatic system



Hodgkin Lymphoma classically presents as a painless, non-tender, firm, rubbery enlargement of superficial lymph nodes, most often in the cervical region.

### Investigations

- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, leukocytosis, platelets normal or increased early, decreased in advanced disease
- biochemistry
  - HIV serology
  - LFTs (liver involvement)
  - RFTs (prior to initiating chemotherapy)
  - ALP, Ca<sup>2+</sup> (bone involvement)
  - ESR, LDH (monitor disease progression)
- imaging
  - CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), gallium scan (assess treatment response)
  - cardiac function assessment (MUGA or echocardiography): for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA), treatment can be cardiotoxic
  - PFTs: if history of lung disease (COPD, smoking, previous radiation to lung)
- excisional lymph node biopsy confirms diagnosis
- bone marrow biopsy to assess marrow infiltration (only necessary if B-symptoms, stage III or IV, bulky disease or cytopenia)

### Treatment

- stage I-II: chemotherapy (ABVD) followed by involved field radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD) with XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy, bone marrow transplant
  - new imaging modalities increasingly used including PET scans used to follow response to treatment

### Complications of Treatment

- cardiac disease: secondary to XRT, adriamycin is also cardiotoxic
- pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
- infertility: recommend sperm banking
- secondary malignancy in irradiated field
  - <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  - solid tumours of lung, breast; >8 yr after treatment
  - non-Hodgkin lymphoma
- hypothyroidism: post XRT



#### Common Chemotherapeutic Regimens

**CHOP:** cyclophosphamide, hydroxydoxorubicin (Adriamycin), vincristine (Oncovin), prednisone

**VAD:** vincristine, adriamycin, dexamethasone

**ABVD:** adriamycin, bleomycin, vinblastine, dacarbazine

**BEACOPP:** bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone

### Prognosis

- Hasenclever adverse prognostic factors:
  - serum albumin  $<40$  g/L (4 g/dL)
  - hemoglobin  $<105$  g/L (10.5 g/dL)
  - male
  - stage IV disease
  - age  $\geq 45$  yr
  - leukocytosis (WBC  $>1.5 \times 10^9$ /L)
  - lymphocytopenia (lymphocytes  $<0.06 \times 10^9$ /L or  $<8\%$  of WBC count or both)
- prognostic score
  - each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)



#### International Prognostic Factors Project 1998

Prognostic Factors	FFP
0	84%
1	77%
2	67%
3	60%
4	51%
5-7	42%

FFP = freedom from progression at 5 yr.

## Non-Hodgkin Lymphoma (NHL)

### Definition

- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

### Classification

- multiple classification systems exist at present and may be used at different centres
- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma
  - T-cell NHL: e.g. mycosis fungoides, anaplastic large cell lymphoma
- WHO/REAL classification system: 3 categories of NHLs based on natural history
  - indolent** (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, mantle cell lymphoma
  - aggressive** (~50% of NHL): e.g. diffuse large B-cell lymphoma
  - highly aggressive** (~5% of NHL): e.g. Burkitt's lymphoma

### Clinical Features

- painless superficial lymphadenopathy, usually  $>1$  lymph node region
- usually presents as widespread disease (exception is aggressive lymphoma)
- constitutional symptoms not as common as in Hodgkin lymphoma
- cytopenia: anemia  $\pm$  neutropenia  $\pm$  thrombocytopenia can occur when bone marrow is involved
- abdominal signs
  - hepatosplenomegaly
  - retroperitoneal and mesenteric involvement (2nd most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement: most commonly GI tract; also testes, bone, kidney
- CNS involvement in 1% (often with HIV)



#### NHL: Associated Conditions

- Immunodeficiency (e.g. HIV)
- Autoimmune diseases (e.g. SLE)
- Infections (e.g. EBV)

### Investigations

- CBC:
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia
  - advanced disease: thrombocytopenia, neutropenia and leukoerythroblastic anemia
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood is valuable for low-grade NHL
- biochemistry:
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease, poor prognostic factor)
- CXR, CT neck, abdomen, pelvis for staging
- PET is useful for monitoring response to treatment and evaluation of residual tumour following therapy in aggressive histological disease
- diagnosed by:
  - lymph node biopsy: excisional biopsy preferred, FNA unreliable
  - bone marrow biopsy: not optimal for diagnosis as BM may not be involved

### Treatment

- localized disease (e.g. GI, brain, bone, head and neck)
  - radiotherapy to primary site and adjacent nodal areas
  - adjuvant chemotherapy
  - surgery: splenic marginal zone lymphoma
- indolent lymphoma:** goal of treatment is symptom management
  - watchful waiting
  - radiation therapy for localized disease
  - CHOP + rituximab, an anti-CD20 antibody (CHOP-R) for advanced stage disease



#### CHOP-Like Chemotherapy with or without Rituximab in Young Patients with Good-Prognosis Diffuse Large B-Cell Lymphoma (MInT)

*Lancet Oncol* 2011;12:1013-1022

**Study:** International RCT with a median follow-up of 72 mo.

**Participants:** 824 patients with good-prognosis diffuse large B-cell lymphoma who had  $\leq 1$  risk factor, stage II-IV disease or stage I disease with bulky (age: 18 to 60 yr).

**Intervention:** Patients received either 6 cycles of CHOP-like chemotherapy and rituximab (CCR;  $n=413$ ) or 6 cycles of CHOP-like chemotherapy alone (CLC;  $n=411$ ). Bulky and extranodal sites received additional radiotherapy.

**Primary Outcome:** Event-free survival.

**Results:** Patients receiving CCR had an increased 6-yr event-free survival compared with the CLC group (74.3% vs. 55.8%;  $p<0.0001$ ). Event-free survival was affected by treatment group, presence of bulky disease, and age-adjusted International Prognostic Index (IPI). Overall survival was affected by treatment group and presence of bulky disease. Within the CCR group, a favourable subgroup (IPI=0, no bulky) and less favourable subgroup (IPI=1 or bulky, or both) could be defined; event-free survival was 84.3% vs. 71.0%.

**Conclusion:** Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large B-cell lymphoma. The definition of two prognostic subgroups allows a more refined therapeutic approach to these patients than does assessment by IPI alone.

- **aggressive lymphoma:** goal of treatment is curative
  - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  - radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites involved (testicular, nasopharyngeal)
  - relapse, resistant to therapy: high dose chemotherapy, BMT
- **highly aggressive lymphoma**
  - Burkitt Lymphoma: short bursts of intensive chemotherapy
  - “CODOX-M” chemotherapy regimen also often used  $\pm$  IVAC
  - CNS prophylaxis and tumour lysis syndrome prophylaxis



Treatment of HL depends on stage; treatment of NHL depends on histologic subtype.

### Complications

- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- tumour lysis syndrome (particularly in very aggressive lymphoma) – see H50

### Prognosis

- follicular lymphoma: Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60; number of nodal areas >4; elevated LDH; Ann Arbor stage III-IV; hemoglobin <120 g/L
  - based on calculated risk, mean 5 yr survival ranges from 53-91%
  - rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
- diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
  - based on calculated risk, mean 5 yr survival ranges from 26-73%
  - has ~40% rate of cure

**Table 33. Characteristics of Select Non-Hodgkin Lymphomas**

	Follicular Lymphoma	Diffuse Large B-Cell Lymphoma (DLBCL)	Burkitt Lymphoma	Mantle Cell Lymphoma
<b>Percentage of NHLs</b>	22-30%	33%	<1% adult NHLs 30% childhood NHLs	6%
<b>Genetic Mutation</b>	Bcl-2 activation	Bcl-2, Bcl-6, MYC rearrangements	c-myc activation	Overexpression of cyclin D1 (Bcl-1 activation)
<b>Classification</b>	Indolent	Aggressive (high-grade)	Very aggressive	Indolent
<b>Risk Factors</b>	Middle-age – elderly	Previous CLL (Richter's transf.: 5% CLL patients progress to DLBCL)	1. Endemic: African origin, EBV-associated 2. Sporadic: no EBV 3. HIV-related: AIDS-defining illness	Male (male:female = 4:1)
<b>Clinical Features</b>	<ul style="list-style-type: none"> <li>• Widespread painless LAD* <math>\pm</math> bone marrow involvement</li> <li>• Frequent transformation to aggressive lymphoma</li> <li>• Very responsive to chemoradiation tx</li> </ul>	<ul style="list-style-type: none"> <li>• Rapidly progressive LAD and extranodal infiltration</li> <li>• 50% present at stage I/II, 50% widely disseminated</li> </ul>	<ul style="list-style-type: none"> <li>• Endemic form: massive jaw LAD</li> <li>• “Starry-sky” histology</li> <li>• High risk of tumour lysis syndrome upon treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Often presents Stage IV with palpable LAD</li> <li>• Involvement of GI tract (lymphomatosis polyposis), Waldeyer's Ring</li> <li>• Extremely aggressive, 5-yr survival 25%</li> </ul>

\*LAD = lymphadenopathy

## Malignant Clonal Proliferations of Mature B-Cells

**Table 34. Characteristics of B-Cell Malignant Proliferation**

	CLL	Macroglobulinemia	Myeloma
<b>Cell Type</b>	Lymphocyte	Plasmacytoid	Plasma cell
<b>Protein</b>	IgM if present	IgM	IgG, A, light chain (rarely M, D or E)
<b>Lymph Nodes</b>	Very common	Common	Rare
<b>Hepatosplenomegaly</b>	Common	Common	Rare
<b>Bone Lesions</b>	Rare	Rare	Common
<b>Hypercalcemia</b>	Rare	Rare	Common
<b>Renal Failure</b>	Rare	Rare	Common
<b>Immunoglobulin Complications</b>	Common	Rare	Rare



Rouleaux formation on peripheral blood smear, if not artifact, denotes hyperglobulinemia (but not necessarily monoclonality).



## Chronic Lymphocytic Leukemia (CLL)

### Definition

- indolent disease characterized by clonal malignancy of mature B-cells

### Epidemiology

- most common leukemia in Western world
- mainly older patients; median age 65 yr
- M>F

### Pathophysiology

- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes and spleen

### Clinical Features

- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms ( $\geq 1$  of: unintentional weight loss  $\geq 10\%$  of body weight within previous 6 mo, temperature  $>38^\circ\text{C}$  or night sweats for  $\geq 2$  wk without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (Coombs positive), ITP, hypogammaglobulinemia  $\pm$  neutropenia
- bone marrow failure: late, secondary to marrow involvement by CLL cells

### Investigations

- CBC: absolute lymphocytes  $>5 \times 10^9/\text{L}$  with a CLL phenotype
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry (CD5, CD20, CD23, etc.)
- cytogenetics: FISH (dictates response to therapy and prognosis)
- bone marrow aspirate
  - lymphocytes  $>30\%$  of all nucleated cells
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis) or mixed (25%)



Smudge cells are artifacts of damaged lymphocytes from slide preparation.

### Natural History and Treatment

- natural history: indolent but incurable, with slow progression; thus select gentlest treatment that will control symptoms
  - observation if early, stable, asymptomatic
  - intermittent chlorambucil or fludarabine chemotherapy combined with rituximab, chlorambucil in the elderly
  - corticosteroids, IVIG: especially for autoimmune phenomena
  - radiotherapy
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- 9 yr median survival, but varies greatly



- prognosis predicted by Rai staging
  - low risk: lymphocytosis in blood and bone marrow only
  - intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
  - high risk: lymphocytosis with disease-related anemia ( $<110$  g/L) or thrombocytopenia ( $<100 \times 10^9/L$ )

### Complications

- bone marrow failure
- immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia, impaired T-cell function)
- polyclonal or monoclonal gammopathy (often IgM)
- hyperuricemia with treatment
- 5% undergo Richter's transformation: aggressive transformation to diffuse large B-cell lymphoma (see Table 33)

## Multiple Myeloma (MM)



### Definition

- neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
- usually single clone of plasma cells, although biclonal myeloma also occurs. Rarely non-secretory

### Epidemiology

- incidence 3 per 100,000, most common plasma cell malignancy
- increased frequency with age; median age of diagnosis is 68 yr; M>F

### Pathophysiology

- malignant plasma cells secrete monoclonal antibody
  - 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    - ♦ IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    - ♦ 15-20% produce free light chains or light chains alone found in either:
      - serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      - urine has Bence-Jones protein
  - <5% are non-secretors

### Clinical Features and Complications

- bone disease: pain (usually back), bony tenderness, pathologic fractures
  - lytic lesions are classical (skull, spine, proximal long bones, ribs)
  - increased bone resorption secondary to osteoclast activating factors such as PTHrP
- anemia: weakness, fatigue, pallor
  - secondary to bone marrow suppression
- weight loss
- infections
  - usually *S. pneumoniae* and Gram-negatives
  - secondary to suppression of normal plasma cell function
- hypercalcemia: N/V, confusion, constipation, polyuria, polydipsia
  - secondary to increased bone turnover
- renal disease/renal failure
  - most frequently causes cast nephropathy (see [Nephrology](#), NP30)
- bleeding
  - secondary to thrombocytopenia, may see petechiae, purpura
  - can also be caused by acquired von Willebrand disease
- extramedullary plasmacytoma
  - soft tissue mass composed of monoclonal plasma cells, purplish colour
- hyperviscosity: may manifest as headaches, stroke, angina, MI
  - secondary to increased viscosity caused by M protein
- amyloidosis
  - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
- neurologic disease: muscle weakness, pain, paresthesias
  - radiculopathy caused by vertebral fracture, extramedullary plasmacytoma
  - spinal cord compression (10-20% of patients) is a medical emergency



### Multiple Myeloma

#### CRAB

Increased Calcium

Renal failure

Anemia

Bony lesions (lytic lesions or osteoporosis felt to be caused by myeloma)



Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis.



### Amyloid

The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues.

Found in a variety of clinical disorders and can cause systemic [e.g. MM (light chains)] or localized amyloidosis [e.g. Alzheimer disease (AB amyloid)].

## Investigations

- CBC:
  - normocytic anemia, thrombocytopenia, leukopenia
  - rouleaux formation on peripheral film
- biochemistry:
  - increased  $\text{Ca}^{2+}$ , increased ESR, decreased anion gap, increased Cr, albumin,  $\beta_2$ -microglobulin (as part of staging), proteinuria (24 h urine collection)
- monoclonal proteins:
  - serum protein electrophoresis (SPEP): demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - urine protein electrophoresis (UPEP): demonstrates light chains in urine = Bence-Jones protein (15% only secrete light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- bone marrow aspirate and biopsy
  - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for FISH or cytogenetics (prognostic implications)
- skeletal series (x-rays), MRI if symptoms of cord compression
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
- $\beta_2$ -microglobulin, LDH and CRP are poor prognosticators



### Light Chain Disease

15% of MM produce only light chains. Renal failure is a major problem. Kappa > lambda light chain has better prognosis.

## Diagnosis

- International Myeloma working group criteria
  1. serum or urinary monoclonal protein
  2. presence of clonal plasma cells in bone marrow or a plasmacytoma
  3. presence of end-organ damage related to plasma cell dyscrasia, such as:
    - ♦ increased serum  $\text{Ca}^{2+}$
    - ♦ lytic bone lesions
    - ♦ anemia
    - ♦ renal failure

## Treatment

- treatment is non-curative
- treatment goals:
  - improvement in quality of life (improve anemia, reverse renal failure, bony pain)
  - prevention of progression and complications
  - increase overall survival
- autologous stem cell transplant if <65 yr old
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents (i.e. IMiDs or proteasome inhibitors)
- chemotherapy if >65 yr old or transplant-ineligible
  - melphalan, prednisone and novel agent (i.e. bortezomib)
- dexamethasone and bortezomib if ARF; bortezomib  $\pm$  dexamethasone in light chain amyloidosis
- supportive management:
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia, DVT prophylaxis
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities and preferences

## Prognosis

- International Staging System ( $\beta_2$ -microglobulin and albumin) used to stage and estimate prognosis
  - cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy)
- median survival based on stage, usually 16-70 mo

## Monoclonal Gammopathy of Unknown Significance (MGUS)

### Definition

- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr of age
  - asymptomatic

### Diagnosis

- presence of a serum monoclonal protein (M-protein) at a concentration <30 g/L
- <10% plasma cells in bone marrow
- absence of hyperCalcemia, Renal insufficiency, Anemia, Bony disease related to the plasma cell proliferative process (absence of "CRAB")
- 0.3-1% of patients develop a hematologic malignancy each year
  - patients with M protein peak  $\geq 15$  g/L or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with serum free light chains are at increased risk of malignant transformation
- monitor with annual history, physical, CBC, Cr, calcium, albumin, serum protein electrophoresis (considered pre-malignant)

## Lymphoplasmacytic Lymphoma (Waldenstrom's Macroglobulinemia)

### Definition

- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein

### Clinical Features

- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
- key complication to avoid: hyperviscosity syndrome (see below)
  - because IgM (unlike IgG) confined largely to intravascular space

### Investigations and Diagnosis

- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- bloodwork rarely see hypercalcemia
- cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present

### Management

- R-CVP, alkylating agents (chlorambucil), nucleoside analogues (fludarabine), thalidomide, rituximab, or combination therapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM



#### Serum Free Light Chain Ratio is an Independent Risk Factor for Progression in MGUS

*Blood* 2005;106:812-817

**Purpose:** To determine whether the presence of monoclonal free kappa or lambda immunoglobulin light chains in MGUS increases the risk of progression to malignancy.

**Methods:** Retrospective study with median follow-up of 15 yr. Baseline serum samples obtained from 1383 MGUS patients seen at the Mayo clinic between 1960-1994. 1148 baseline samples were obtained within 30 d of diagnosis.

**Results:** Malignant progression had occurred in 87 (7.6%) patients. In 379 (33%) patients, an abnormal serum free light chain (FLC) ratio was detected. There was a significantly higher risk of progression in patients with an abnormal FLC ratio relative to patients with a normal ratio (hazard ratio, 3.5; 95% CI, 2.3-5.5;  $p < 0.001$ ). This finding was independent of the size and type of the serum monoclonal (M) protein. In high-risk MGUS patients [abnormal serum FLC ratio, non-IgG MGUS, high serum M protein level ( $\geq 1.5$  gm/dL)], the risk of progression at 20 yr was 58% compared to 37% in high-intermediate-risk MGUS (two risk factors), 21% low-intermediate risk (with one risk factor) and 5% low-risk (no risk factors).

**Conclusions:** The presence of an abnormal FLC ratio is a clinically and statistically significant predictor of progression in MGUS. The low-risk subset of patients with MGUS accounts for 40% of all MGUS patients and have a small lifetime risk of progression, thus less follow-up can be justified.



Waldenstrom's macroglobulinemia accounts for 85% of all cases of hyperviscosity syndrome.

## Complications of Hematologic Malignancies

### Hyperviscosity Syndrome

#### Definition

- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum Igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases

**Clinical Features**

- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

**Treatment**

- plasmapheresis, chemotherapy

## Tumour Lysis Syndrome

**Definition**

- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)

**Clinical Features**

- metabolic abnormalities
  - cells lyse, releasing  $K^+$ , uric acid,  $PO_4^{3-}$  (increased levels)
  - $PO_4^{3-}$  binds  $Ca^{2+}$  (decreased  $Ca^{2+}$ )
- complications
  - lethal cardiac arrhythmia (increased  $K^+$ )
  - acute renal failure (urate nephropathy, see [Nephrology](#), NP30)

**Treatment**

- prevention
  - aggressive IV hydration
  - alkalinization of the urine
  - allopurinol or rasburicase
  - correction of pre-existing metabolic abnormalities
- dialysis



## Blood Products and Transfusions

### Blood Products

- RBCs, platelets and coagulation factors (frozen plasma [FP], cryoprecipitate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and platelet-rich plasma
  - platelet-rich plasma is further fractionated into platelets and plasma
    - ♦ need to pool together multiple units to obtain therapeutic amounts
    - ♦ FP (previously known as FFP) is plasma frozen within 24 h of collection
    - ♦ cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures

**Specialized Products**

- irradiated blood products
  - prevent proliferation of donor T-cells in potential or actual BMT recipients
  - used for immunocompromised patients or for patients on purine analogue chemotherapy, first-degree relatives, HLA-matched products and intrauterine transfusions
- CMV-negative blood products
  - potential transplant recipients
  - neonates
  - AIDS patients
  - seronegative pregnant women

**Blood Groups**

Group	Antigen (on RBC)	Antibody (in serum)
O	H	Anti-A, anti-B
A	A	Anti-B
B	B	Anti-A
AB	A and B	Nil



In Canada, blood products are leukodepleted via filtration immediately after donation. Therefore it is considered:

- Low in lymphokines, resulting in a lower incidence of febrile nonhemolytic transfusion reactions
- CMV negative (because CMV is found in leukocytes)

## Red Blood Cells

### Packed Red Blood Cells

- stored at 4°C
- transfuse within 42 d of collection, otherwise cell lysis may result in hyperkalemia
- infuse each unit over 2 h, max of 4 h

### Indications for packed RBC Transfusion

- Hb <70 g/L (7 g/dL); this may change as per patient's tolerance or symptoms
  - maintain Hb between 70 and 100 g/L during active bleeds (7 g/dL to 10 g/dL)
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding
  - impaired pulmonary function
  - increased O<sub>2</sub> consumption

### Selection of Red Cells for Transfusion

- when a need for RBC transfusion is anticipated, the following should be ordered:
  - group and screen
    - ♦ determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens in the patient's serum
  - crossmatch
    - ♦ involves mixing the recipient's blood with potential donor blood and looking for agglutination
    - ♦ takes 30-45 min
- when blood is required, several options are available
  - 1st line: fully crossmatched blood (not always available in emergency situations)
  - 2nd line: donor blood of the same group and Rh status as the recipient
  - 3rd line: O- blood for females of reproductive age; O+ blood for all others



1 unit of pRBC will increase Hb by approximately 10 g/L or increase Hct by 4%.



#### Transfusion Requirements in Critical Care (TRICC)

*NEMJ* 1999;340:409-417

**Study:** Multicentre, RCT.

**Participants:** 838 critically ill patients with euvolemia after initial treatment and hemoglobin less than 9 g/dL within 72 h of ICU admission.

**Intervention:** Patients receiving a transfusion followed either (1) a restrictive strategy (RS; n=418) in which red cells were transfused if hemoglobin was less than 7.0 g/dL and then maintained at 7 to 9 g/dL or (2) a liberal strategy (LS; n=420) in which transfusions occurred when the hemoglobin was less than 10.0 g/dL and then maintained at 10 to 12 g/dL.

**Primary Outcome:** Mortality at 30 d and severity of organ dysfunction.

**Results:** Mortality rates at 30 d were similar between groups. However, mortality rates were significantly lower with the RS among less acutely ill patients (8.7% and RS group and 16.1% in LS group; P=0.03) and among those less than 55 yr of age (5.7% RS and 13% LS; P=0.02), but did not differ in a subgroup with clinically significant cardiac disease.

**Conclusion:** A RS of red cell transfusion is at least as effective as, and possibly superior to, a LS transfusion in critically ill patients.

## Platelets

**Table 35. Platelet Products**

Product	Indication
Random donor (pooled)	Thrombocytopenia with bleeding
Single donor platelets	Potential BMT recipients
HLA matched platelets	Refractory to pooled or single donor platelets, presence of HLA antibodies

- stored at 20-24°C
- random donor platelets are transfused from a pool of 4 units; this should increase the platelet count by  $\geq 15 \times 10^9/L$
- single donor platelets (transfused as single units) should increase the platelet count by  $40-60 \times 10^9/L$
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies, consumption (bleeding, sepsis) or hypersplenism may be present

**Table 36. Indications for Platelet Transfusion**

Plt ( $\times 10^9/L$ )	Indications
<10	Non-immune thrombocytopenia
<20	Procedures not associated with significant blood loss
<50	Procedures associated with blood loss or major surgery (>500 mL EBL)
<100	Pre-neurosurgery or head trauma
Any	Platelet dysfunction (or antiplatelet agents) and marked bleeding

### Relative Contra-indications of Platelet Transfusion

- TTP, HIT, post-transfusion purpura, HELLP

## Coagulation Factors

**Table 37. Coagulation Factor Products**

Product	Indication
Frozen plasma (FP)	Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose
Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII)	Factor VIII deficiency von Willebrand's disease Hypofibrinogenemia
Hemate P	von Willebrand's disease
Factor VIII concentrate	Factor VIII deficiency (Hemophilia A)
Factor IX concentrate	Factor IX deficiency (Hemophilia B)
Recombinant VIIa	Factor VII deficiency with bleeding, Hemophilia A or B with inhibitors
Prothrombin Complex (Octaplex®)	Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (<6 h) surgical procedure

## Acute Blood Transfusion Reactions

### IMMUNE

#### Acute Hemolytic Transfusion Reactions (AHTR)

- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation
- most commonly due to incorrect patient identification
- occurs immediately after transfusion
- risk per unit of blood is <1 in 40,000
- presents with fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

#### Febrile Nonhemolytic Transfusion Reactions (FNHTR)

- due to alloantibodies to WBC, platelets or other donor plasma antigens and release of cytokines from blood product cells
- occurs within 0-6 h of transfusion
- risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <38°C, continue with transfusion but decrease rate and give antipyretics
  - if temperature >38°C, stop transfusion, give antipyretics and anti-histamine

#### Allergic Nonhemolytic Transfusion Reactions

- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1 in 100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenhydramine, steroids, epinephrine, IV fluids and bronchodilators

#### Transfusion-Related Acute Lung Injury (TRALI)

- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - insidious, acute onset of pulmonary insufficiency
  - profound hypoxemia ( $\text{PaO}_2/\text{FiO}_2 < 300$  mmHg)
  - bilateral pulmonary edema on CXR
  - pulmonary artery wedge pressure <18 mmHg
  - no clinical evidence of left atrial hypertension
- pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 h post transfusion and resolves in 24-72 h
- risk per unit of blood is 1:10,000
  - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
- inform blood bank; patient and donor testing will be arranged



#### DDx of Post-Transfusion Fever:

- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction
- Bacterial contamination
- Allergy

#### DDx of Post-Transfusion Dyspnea:

- Circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Allergy (bronchospasm/anaphylaxis)



**NONIMMUNE****Bacterial Infection**

- Gram positive: *S. aureus*, *S. epidermidis*, *Bacillus cereus*
- Gram negative: *Klebsiella*, *Serratia*, *Pseudomonas*, *Yersinia*
- overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids

**Transfusion Associated Circulatory Overload (TACO)**

- due to impaired cardiac function and/or excessive rapid transfusion
- presents as dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung and increased venous pressure
- incidence is 1 in 700
- treatment: transfuse at lower rate, give diuretics and oxygen

**Hyperkalemia**

- due to K<sup>+</sup> release from stored RBC
- risk increases with storage time and if blood is irradiated
- decreased risk if given fresh blood
- occurs in 5% of massively transfused patients
- treatment: see [Nephrology](#), NP13

**Citrate Toxicity**

- occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca<sup>2+</sup> and causes signs and symptoms of hypocalcemia
- treatment: IV calcium gluconate (10 mL of 10%) for every 2 units of blood

**Dilutional Coagulopathy**

- occurs with massive transfusion (>10 units)
- pRBC contains no clotting factors, fibrinogen, cryoprecipitate or platelets
- treatment: FP, platelets and cryoprecipitate

## Delayed Blood Transfusion Reactions

**IMMUNE****Delayed Hemolytic**

- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
- occurs 5-7 d after transfusion
- presents as anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion

**Transfusion-Associated Graft Versus Host Disease (GVHD)**

- transfused T-lymphocytes recognize and react against “host” (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- presents as fever, diarrhea, liver function abnormalities and pancytopenia
- can be prevented by giving irradiated blood products

**NONIMMUNE****Iron Overload**

- due to repeated transfusions over long period of time (e.g.  $\beta$ -thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if not longer requiring blood transfusion and not anemic

**Viral Infection Risk**

- HBV <1 in 153,000
- Human T-lymphotropic virus (HTLV) <1 in 4,300,000
- HCV <1 in 2,300,000
- HIV <1 in 7,000,000
- other infections include EBV, CMV, WNV (West Nile virus)

# Common Medications

## Antiplatelet Therapy

- see Figure 12a, *Platelet Activation Cascade*, H24

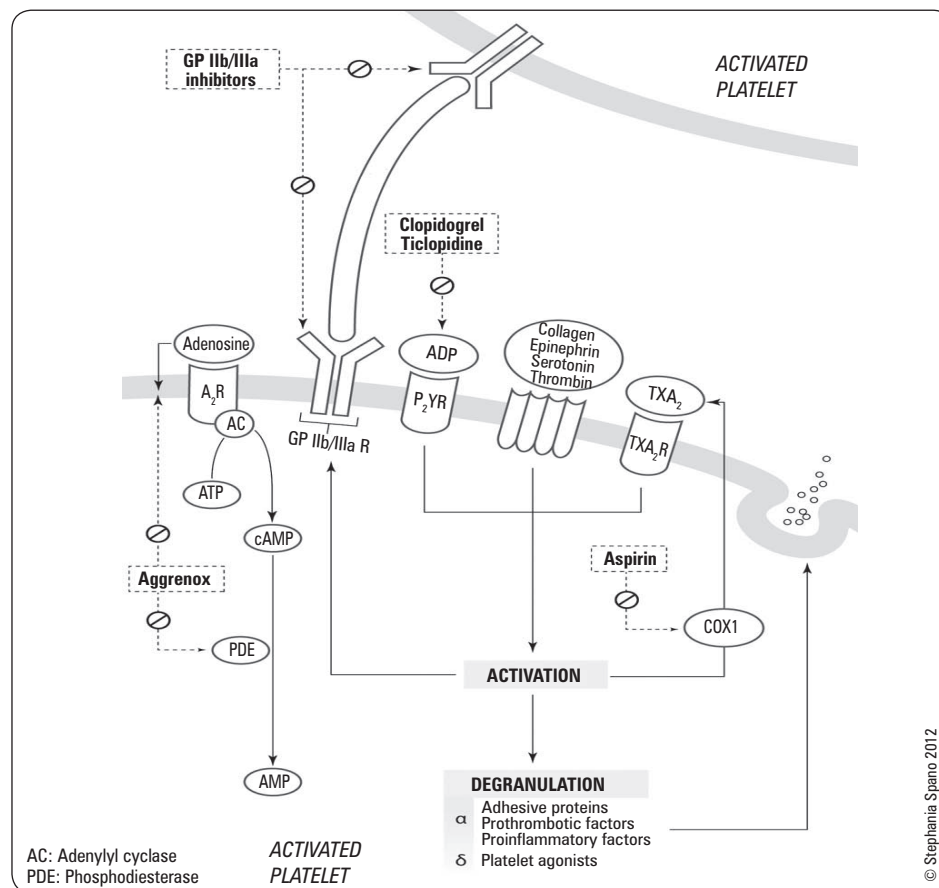


Figure 16. Mechanisms of action of antiplatelet therapy

Table 38. Antiplatelet Therapy

	Mechanism of Action	Dose/Route of Administration	Onset/Peak/Duration	Specific Side Effects	Remarks
Aspirin® (ASA)	Irreversibly acetylates COX, inhibiting TXA <sub>2</sub> synthesis, thus inhibiting platelet aggregation	Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily	Onset: 5-30 min Peak: 0.25-3 h Duration: 3-6 h	GI ulcer/bleeding Tinnitus Bronchospasm Angioedema Reye's syndrome in pediatric patients	Indicated for stroke/MI prophylaxis Reduce incidence of recurrent MI Decrease mortality in post-MI patients Contraindicated in patients with GI ulcers
Aggrenox® (ASA + dipyridamole)	Dipyridamole increases intracellular cAMP levels, which inhibits TXA <sub>2</sub> synthesis, leading to decreased platelet aggregation	1 capsule PO bid	Peak: 75 min	Headache Dyspepsia Nausea/vomiting Abdominal pain Cardiac failure Hemorrhoids	More effective than ASA in secondary prevention of stroke Dipyridamole potentiates antiplatelet action of ASA
Clopidogrel (Plavix®)	Inhibit ADP binding to platelets, thus decreased platelet aggregation	75-300 mg PO daily	Onset: 2 h Peak: 1 h	URI Chest pain Headache Flu-like syndrome Depression UTI GI hemorrhage Pancytopenia May cause TTP	Prevention of cardiovascular events in high-risk patients CYP2C19 poor metabolizers have diminished response to clopidogrel Caution with hepatic/renal impairment
Glycoprotein IIb/IIIa inhibitors [Reopro® (abciximab), Integrelin® (epti)]	Blocking GP II/IIIa receptor inhibits fibrinogen and vWF binding, leading to decreased platelet aggregation	Variable IV	Variable	Hypotension Back pain Nausea/vomiting Chest pain Abdo pain Thrombocytopenia	Used most commonly in cardiac catheterization Contraindicated in PUD Monitoring aPTT/activated clotting time



### Antiplatelet/Anticoagulation and Pregnancy

#### Class A:

- None

#### Class B:

- Argatroban
- Fondaparinux
- Clopidogrel
- LMWH

#### Class C:

- ASA (1st and 2nd trimesters)
- Heparin
- Dabigatran
- Abciximab
- Rivaroxaban

#### Class D:

- ASA (in 3rd trimester)
- Aggrenox
- Warfarin (warfarin embryopathy)

#### Class E:

- None

## Anticoagulant Therapy

**Table 39. Anticoagulant Therapy**

	Mechanism of Action	Dose/Route of Administration	Onset/Peak/Duration	Reversing Agent	Monitoring	Specific Side Effects	Remarks
Heparin	Accelerates activity of antithrombin	As per hospital nomogram	Onset: 20-60 min Peak: 2-4 h	Protamine sulphate	aPTT (intrinsic pathway), UFH (anti-Xa) levels	Hemorrhage HIT Increased liver enzymes	Pregnancy: safe (does not cross placenta)
Warfarin	Vitamin K antagonist: inhibits production of II, VII, IX, X, proteins C and S	Individualized dosing by monitoring PT/INR PO	Onset: 36-48 h Peak: 1.5-3 d	IV vitamin K PCC FFP	PT/INR maintain 2-3 (2.5-3.5 for mechanical valves)	Hemorrhage Cholesterol embolism syndrome Intraocular hemorrhage	Pregnancy: not used, can cross placenta (teratogenic)
LMWH (enoxaparin, dalteparin, tinzaparin)	Inhibits FXa	Variable SC/IV	Onset: 3-5 h Peak: 3-5 h Duration: 12 h	Partial reversibility with protamine sulphate	FXa in pediatrics, pregnancy and weight > 150 kg	Hemorrhage Fever Increased liver enzymes <1% HIT	Increased bioavailability than heparin Can accumulate in patients low CrCl (<30)
Fondaparinux	Selective inhibitor of FXa	Variable SC daily	Onset: 2 h Peak: 2-3 h	Not reversible	None	Anemia Fever Nausea Rash	Heparin analogue Contraindicated in renal failure
Rivaroxaban	Anti-FXa	PO	Peak: 2-4 h	Not reversible	None	Syncope GI hemorrhage	Only indicated in treatment of acute VTE (not in cancer patients), and thromboprophylaxis in orthopedic patients
Argatroban	Direct thrombin inhibitor	Variable IV	Onset: 5-10 min Duration: 20-40 min	Not reversible	aPTT	Dyspnea Hypotension Fever	Indicated for HIT, renal failure, unstable patients
Dabigatran	Direct thrombin inhibitor	150 mg PO bid	Peak: 1 h	Not reversible	None (prolonged aPTT can suggest residual drug on board)	GI upset Dyspepsia	Only indicated for AFib in Canada Contraindicated in renal failure, cancer patients, mechanical heart valves

### Adverse Reactions of Heparin

- hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- heparin-induced thrombocytopenia: associated with venous or arterial thrombosis (see Table 22, H27)
- osteoporosis: with long term use

### Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)

- increased bioavailability compared to normal heparin
- increased duration of action
- SC route of administration
- do not need to monitor aPTT
- adverse reactions less common than UFH
- patients with renal failure (CrCl <30) can accumulate LMWH, therefore must adjust dose
- only partially reversible with protamine sulphate

**Table 40. Recommended Therapeutic INR Ranges of Common Indications for Oral Anticoagulant Therapy**

Indication	INR Range
Prophylaxis of venous thrombosis (high-risk surgery)	2.0-3.0
Treatment of venous thrombosis	
Most cases of thrombosis with antiphospholipid antibody syndrome	
Treatment of pulmonary embolism	
Prevention of systemic embolism	
Tissue heart valves	
AMI (to prevent systemic embolism)	
Valvular heart disease	
Atrial fibrillation	
Bileaflet mechanical valve in aortic position	
Mechanical prosthetic mitral valves (high risk)	2.5-3.5
Prophylaxis of recurrent myocardial infarction	

AMI = acute myocardial infarction



#### Dabigatran versus Warfarin in Patients with Atrial Fibrillation

*NEMJ* 2009;361:1139-1151

**Study:** Non-inferiority trial with 2-yr follow-up.

**Methods:** Random assignment of 18,113 patients with atrial fibrillation and risk of stroke to fixed doses of dabigatran (blinded, 110 mg or 150 mg bid) or adjusted-dose warfarin (unblinded). Primary outcome was stroke or systemic embolism.

**Results:** The warfarin, dabigatran 110 mg, and dabigatran groups showed the following rates: 1) stroke or systemic embolism was 1.69%, 1.53%, and 1.11% per year respectively, 2) major bleeding was 3.36%, 2.71%, and 3.11% per year respectively, 3) hemorrhagic stroke was 0.38%, 0.12%, 0.10% per year respectively ( $p < 0.001$ ), 4) mortality was 4.13%, 3.75%, and 3.64% respectively.

**Conclusions:** In patients with atrial fibrillation, dabigatran 110 mg was similar to warfarin in rates of stroke and systemic embolism but had lower rates of major hemorrhage. Dabigatran 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

**Table 41. Recommended Management of a Supratherapeutic INR**

INR	Bleeding Present	Recommended Action
>Therapeutic to 4.5	No	Lower warfarin dose, <b>OR</b> Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range, <b>OR</b> No dose reduction needed if INR is minimally prolonged
>4.5 to 10.0	No	Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range, <b>OR</b> Omit a dose and administer 1 to 2.5 mg oral vit K in patients with increased risk of bleeding
>10.0	No	Hold warfarin and administer 5 to 10 mg oral vit K. Monitor INR more frequently and administer more vit K as needed. Resume warfarin at a lower dose when INR is in therapeutic range
Any	Serious or life threatening	Hold warfarin and administer 10 mg vit K by slow IV infusion; supplement with four-factor prothrombin complex concentrate. Monitor and repeat as needed

Adapted from: Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;(2 suppl):e152S

## Chemotherapeutic and Biologic Agents Used in Oncology

**Table 42. Selected Chemotherapeutic and Biologic Agents**

Class	Example	Mechanism of Action or Target
<b>Alkylating Agent</b>	<ul style="list-style-type: none"> <li>chlorambucil, cyclophosphamide, melphalan (nitrogen mustards)</li> <li>carboplatin, cisplatin</li> <li>dacarbazine, procarbazine</li> <li>busulfan</li> </ul>	Damage DNA via alkylation of base pairs Leads to cross-linking of bases, abnormal base-pairing, DNA breakage
<b>Antimetabolites</b>	<ul style="list-style-type: none"> <li>methotrexate (folic acid antagonist)</li> <li>6-mercaptopurine, fludarabine (purine antagonist)</li> <li>5-fluorouracil (5-FU) (pyrimidine antagonist)</li> <li>hydroxyurea</li> <li>cytarabine</li> </ul>	Inhibit DNA synthesis
<b>Antibiotics</b>	<ul style="list-style-type: none"> <li>adriamycin (anthracycline)</li> <li>bleomycin</li> <li>mitomycin C</li> <li>daunorubicin</li> </ul>	Interfere with DNA and RNA synthesis
<b>Taxanes</b>	<ul style="list-style-type: none"> <li>paclitaxel</li> <li>docetaxel</li> </ul>	Stabilize microtubules against breakdown once cell division complete
<b>Vinca-alkaloids</b>	<ul style="list-style-type: none"> <li>vinblastine</li> <li>vincristine</li> <li>vinorelbine</li> </ul>	Inhibit microtubule assembly (mitotic spindles), blocking cell division
<b>Topoisomerase Inhibitors</b>	<ul style="list-style-type: none"> <li>irinotecan, topotecan (topo I)</li> <li>etoposide (topo II)</li> </ul>	Interfere with DNA unwinding necessary for normal replication and transcription
<b>Steroids</b>	<ul style="list-style-type: none"> <li>prednisone</li> <li>dexamethasone</li> </ul>	Immunosuppression
<b>Monoclonal Antibodies</b>	<ul style="list-style-type: none"> <li>trastuzumab (Herceptin®)</li> <li>bevacizumab (Avastin®)</li> <li>rituximab (Rituxan®)</li> <li>cetuximab (Erbix®)</li> </ul>	HER2 VEGF CD20 EGFR
<b>Small Molecule Inhibitors</b>	<ul style="list-style-type: none"> <li>imatinib mesylate (Gleevec®)</li> <li>dasatinib</li> <li>nilotinib</li> <li>erlotinib (Tarceva®)</li> <li>gefitinib (Iressa®)</li> <li>bortezomib (Velcade®)</li> <li>sunitinib (Sutent®)</li> </ul>	<i>Bcr-Abl</i> <i>Bcr-Abl</i> <i>Bcr-Abl</i> EGFR EGFR 26S proteasome VEGFR, PDGFR

## Landmark Hematology Trials

Trial	Reference	Results
AZA-001	<i>Lancet Oncol</i> 2009; 10:223-32	Azacitidine increases overall survival in higher-risk myelodysplastic syndrome than conventional care
CHOP	<i>NEJM</i> 1993; 328:1002-6	In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival. CHOP is the standard for advanced NHL
CLL8	<i>Lancet</i> 2010; 376:1164-74	Rituximab plus fludarabine and cyclophosphamide (FCR) improves progression-free and overall survival compared with fludarabine and cyclophosphamide alone (FC) in the treatment of CLL
CLOT	<i>NEJM</i> 2003; 349:146-53	In patients with cancer and acute venous thromboembolism, LWMH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding
CML: Imatinib vs. IFN + Cytarabine	<i>NEJM</i> 2003; 348:994-1004	In patients with chronic-phase CML, imatinib was more effective than IFN $\alpha$ + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis
Dabigatran versus warfarin in VTE	<i>NEJM</i> 2009; 361:2342-52	In the treatment of venous thromboembolism, dabigatran is as effective as warfarin and also has a similar safety profile. Note: many problems in the trial, making it less pivotal in having drug approval
Dose of platelet transfusion	<i>NEJM</i> 2010; 362:600-13	Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions but not incidence of bleeding in patients with hypoproliferative thrombocytopenia
ESPIRIT	<i>Lancet</i> 2006; 367:1665-73	ASA plus dipyridamole is recommended over ASA alone as antithrombotic therapy after cerebral ischemia of arterial origin
Hodgkin Lymphoma: ABVD vs. MOPP	<i>NEJM</i> 1992; 327:1478-84	In Hodgkin lymphoma, ABVD regimen has equal failure-free and overall survival to MOPP + ABVD, but less myelotoxicity. ABVD is standard chemotherapy for Hodgkin lymphoma
ITP: Dexamethasone	<i>NEJM</i> 2003; 349:831-6	A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura
MInT Group	<i>Lancet Oncol</i> 2011; 12:1013-1022	Rituximab added to CHOP-like chemotherapy improved long-term outcomes for young patients with good-prognosis DLBCL
MSH	<i>NEJM</i> 1995; 332:1317-22	Hydroxyurea is effective in reduction of complications and clinical manifestations of sickle cell disease
Platelet transfusion threshold	<i>NEJM</i> 1997; 337:1870-5	The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10. Use of the lower threshold reduced platelet usage by 21.5 percent
PT1	<i>NEJM</i> 2005; 353:85-6	Hydroxyurea plus low-dose ASA is superior to anagrelide plus low-dose ASA for patients with essential thrombocythemia at high risk for vascular events
R-CHOP	<i>NEJM</i> 2002; 346:235-42	Addition of rituximab to CHOP increases complete response rate and prolongs event-free survival and overall survival in elderly with DLBCL
Therapeutic platelet transfusion	<i>Lancet</i> 2012; 380:1309-16	Therapeutic platelet transfusions (when bleeding occurs) may be used if severe bleeding can be identified early in autologous stem-cell transplant patients. Prophylactic transfusion (when platelets <10) should remain standard of care in AML patients
TRICC	<i>NEJM</i> 1999; 340:409-17	A restrictive strategy of red-cell transfusion (when Hb <70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb <100) in ICU patients; one possible exception is patients with an acute MI or unstable angina
VISTA	<i>JCO</i> 2010; 28:2259-66	Bortezomib plus melphalan and prednisone (MPV) is superior to melphalan and prednisone (MP) in overall survival of non-transplant-eligible multiple myeloma patients

# References

- Armitage JO. Treatment of Non-Hodgkin's lymphoma. *NEJM* 1993;328:1023-1030.
- Bataille R, Harousseau J. Multiple myeloma. *NEJM* 1997;336:1657-1664.
- Bates SM, Ginsberg JS. Treatment of deep-vein thrombosis. *NEJM* 2004;351:268-277.
- Bazemore AW, Smucker DR. Lymphadenopathy and malignancy. *Am Fam Phys* 2002;66:2103-2110.
- Bottomley SS. Causes of the hereditary and acquired sideroblastic anemias. UpToDate Waltham, MA. 2006.
- Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference Statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008;148:932-938.
- Callum JL. Idiopathic thrombocytopenia purpura. Available from: <http://www.hematology.utoronto.ca/assets/hematology+digital+assets/treatment+and+policies/idiopathic+thrombocytopenia+purpura.pdf>.
- Callum JL, Pinkerton PH. *Bloody easy*, 3rd ed. Toronto: Sunnybrook and Women's College Health Sciences Centre, 2011. Blood transfusions, blood alternatives and transfusion reactions.
- Canadian Pediatric Society. Transfusion and risk of infection in Canada: update 2006. *Ped Child Health* 2005;11:158-162.
- Castellone DD. *Saunders Manual of Clinical Laboratory Science*. Philadelphia: WB Saunders, 1998. Evaluation of bleeding disorders.
- Cecil's essentials of medicine. Thrombocytopenia.
- Christiansen SC, et al. Thrombophilia, clinical factors, and recurrent thrombotic events. *JAMA* 2005;293:2353-2361.
- Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *NEJM* 2002;346:995-1008.
- Coates TD, Baehner RL. Rose BD (Ed). Waltham: UpToDate, 2006. Causes of neutrophilia.
- Cohen K, Scadden DT. Non-Hodgkin's lymphoma: pathogenesis, clinical presentation, and treatment. *Cancer Treat Res* 2001;104:201-203.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *NEJM* 2009;361:1139-1151.
- Decousus et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *NEJM* 1998;338:409-415.
- Driscoll MC. Sickle cell disease. *Ped Rev* 2007;28:259-286.
- Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *NEJM* 2006;355:2408-2417.
- EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *NEJM* 2010; 362:2499-510.
- Eriksson BI, Dahl OE, Rosencranch N, et al. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement; a randomized, double-blind, non-inferiority trial. *Lancet* 2007;379:949-956.
- Eriksson BI, Quinlan DJ, Eikelboom JW. Novel oral factor Xa and thrombin inhibitors in the management of thromboembolism. *Ann Rev Med* 2011;62:41-57.
- Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism. Seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126L:3385-4005.
- George JN. UpToDate, Rose BD (editor). Treatment and prognosis of idiopathic thrombocytopenic purpura. Waltham: UpToDate. 2005.
- Goldman J. ABC of clinical haematology: chronic myeloid leukaemia. *BMJ* 1997;314:657.
- Habermann TM, Steensma DP. Lymphadenopathy. *Mayo Clinic Proc* 2000;75:723-32.
- Hasenclever D, Diehl V, et al. A prognostic score for advanced Hodgkin's disease. International prognostic factors project on advanced hodgkin's disease. *NEJM* 1998;339:1506-1514.
- Health Canada. Effects of lead on human health. Available from: <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/lead-plomb-eng.php>.
- Heaney ML, Golde DW. Myelodysplasia. *NEJM* 1999;340:1649-1660.
- Kovacs MJ, et al. Comparison of 10-mg and 5-mg warfarin initiation monograms together with low-molecular-weight heparin for out patient treatment of acute venous thromboembolism. *Ann Intern Med* 2003;138:714-719.
- Kyle RA, Rajkumar SV. Chemotherapy in multiple myeloma. UpToDate, Rose BD (editor), UpToDate Waltham, MA. 2006.
- Kyle RA, Rajkumar SV. Clinical manifestations and diagnosis of Waldenström's macroglobulinemia. UpToDate, Rose BD (editor), UpToDate Waltham MA. 2006.
- Landaw, SA. Approach to the adult patient with thrombocytopenia. Up To Date, Rose BD (editor), UpToDate, Waltham, MA. 2005.
- Leonardi-Bee J, Bath PM, Boussier MG, et al. Review: dipyridamole given with or without Aspirin® reduces recurrent stroke. *ACP Journal Club* 2005;143:10.
- Liesner RJ, Machin SJ. ABC of clinical haematology: platelet disorders. *BMJ* 1997;314:809.
- Liesner RJ, Goldstone AH. ABC of clinical haematology: the acute leukaemias. *BMJ* 1997;314:733.
- Lowenberg B, Downing JR, Burnett A. Acute myeloid leukemia. *NEJM* 1999;341:1051-1062.
- MabThera International Trial (MInT) Group. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomized study of the MInT Group. *Lancet Oncol* 2011;12:1013-1022.
- Mackie IJ, Bull HA. Normal haemostasis and its regulation. *Blood Rev* 1989;3:237-250.
- Markovic M, et al. Usefulness of soluble transferrin receptor and ferritin in iron deficiency and chronic disease. *Scan J Clin Lab Invest* 2005;65:571-576.
- Mead GM. ABC of clinical haematology: malignant lymphomas and chronic lymphocytic leukaemia. *BMJ* 1997;314:1103.
- Messinezy M, Pearson TC. ABC of clinical haematology: polycythaemia, primary (essential) thrombocythaemia and myelofibrosis. *BMJ* 1997;314:587.
- Mechanisms of severe transfusion reactions. *Transfus Clin Biol* 2001;8:278-281.
- Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011;117:4190-4207.
- Pangalis GA, Vassilakopoulos TP, Boussiotis VA, Fessas P. Clinical approach to lymphadenopathy. *Semin Oncol* 1993;20:570-582.
- Pillot G, Chantler M, Magiera H, et al [editors]. The Washington Manual Hematology and Oncology Subspecialty Consult. Philadelphia: Lippincott Williams & Wilkins, 2004.
- Pui C, Evans WE. Acute lymphoblastic leukemia. *NEJM* 1998;339:605-615.
- Rose BD (editor). Waltham MA. Approach to the patient with thrombocytosis. UpToDate 2009.
- Rozman C, Montserrat E. Chronic lymphocytic leukemia. *NEJM* 1995;333:1052-1057.
- Sabatine MS (editor). Pocket medicine, 2nd ed. The Massachusetts General Hospital Handbook of Internal Medicine. Philadelphia: Lippincott Williams & Wilkins, 2004. Hematology-oncology.
- Satake N, Sakamoto K. Acute lymphoblastic leukemia (internet). E-medicine 2006. Available from: <http://www.emedicine.com/ped/topic2587.html>.
- Sawyers C. Chronic myeloid leukemia. *NEJM* 1999;340:1330-1340.
- Streiff MB, Smith B, Spivak JL. The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: a survey of American Society of Hematology members' practice patterns. *Blood* 2002;99:1144-1149.
- Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *NEJM* 2009;361:2342-2352.
- The Merck Manual. Section 11, Chapter 133: Platelet disorders.
- Thomas RH. Hypercoagulability syndromes. *Arch Intern Med* 2001;161:2433-2439.
- U.S. Consumer Product Safety Commission. Ban of lead-containing paint and certain consumer products bearing lead-containing paint. Available from: <http://www.cpsc.gov/BUSINFO/regsumleadpaint.pdf>.
- Valentine KA, Hull RD. UpToDate, Rose BD (Ed), UpToDate, Waltham, MA. 2006. Clinical use of warfarin.
- Valentine KA, Hull RD. UpToDate, Rose BD (Ed), UpToDate, Waltham MA. 2006. Clinical use of heparin and low molecular weight heparin.
- Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood* 2009;114:937-951.
- Verstovsek S, Mesa RA, Gotlib J, et al. A Double-blind, placebo-controlled trial of ruxolitinib for Myelofibrosis. *NEJM* 2012;366:799-807.
- Wells PS, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *NEJM* 2003;349:1227-1235.
- Wilson SE, Watson HG, Crowther MA. Low-dose oral vitamin K therapy for the management of asymptomatic patients with elevated international normalized ratios: a brief review. *CMAJ* 2004;170:821-824.



Alice Gray and Alissa Visram, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Andrew Morris, Dr. Andrea V. Page, Dr. Susan Poutanen and Dr. Darrell Tan, staff editors

<b>Acronyms</b> .....	2	<i>Candida albicans</i>	
<b>Principles of Microbiology</b> .....	2	<i>Aspergillus</i> spp.	
Bacteriology		<b>Parasitic Infections</b> .....	31
Virology		Protozoa – Intestinal/Genitourinal Infections	
Mycology		<i>Entamoeba histolytica</i> (Amoebas)	
Parasitology		<i>Giardia lamblia</i>	
Transmission of Infectious Diseases		<i>Trichomonas vaginalis</i>	
Prevention of Infectious Diseases		<i>Cryptosporidium</i> spp.	
<b>Nosocomial Infections</b> .....	7	Blood and Tissue Infections	
<b>Respiratory Infections</b> .....	8	<i>Plasmodium</i> spp. (malaria)	
Pneumonia		<i>Trypanosoma cruzi</i>	
Influenza		<i>Toxoplasma gondii</i>	
<b>Skin and Soft Tissue Infections</b> .....	10	Helminths	
Cellulitis		Roundworms – Nematodes	
Necrotizing Fasciitis		Flatworms	
<b>Gastrointestinal Infections</b> .....	11	Cestodes/Trematodes	
Acute Diarrhea		Trematodes/Flukes	
Traveller's Diarrhea		<i>Schistosoma</i> spp.	
Chronic Diarrhea		Ectoparasites	
Peptic Ulcer Disease ( <i>H. pylori</i> )		<b>Travel Medicine</b> .....	36
<b>Bone and Joint Infections</b> .....	15	Fever in the Returned Traveller	
Septic Arthritis		<b>Fever of Unknown Origin (FUO)</b> .....	38
Diabetic Foot Infections		<b>Infections in the Immunocompromised Host.</b> .	39
Osteomyelitis		Febrile Neutropenia (FN)	
<b>Cardiac Infections</b> .....	17	Infections in Solid Organ Transplant Recipients	
Infective Endocarditis (IE)		Immune Reconstitution Syndrome (IRS)	
<b>Neurological Infections</b> .....	19	<b>HIV and AIDS</b> .....	41
Meningitis		Epidemiology	
Encephalitis		Definition and Pathophysiology	
Generalized Tetanus		Modes of Transmission	
Rabies		Natural History	
<b>Systemic Infections</b> .....	22	Laboratory Diagnosis	
Sepsis and Septic Shock		Management of the HIV-Positive Patient	
Tuberculosis (TB)		Highly Active Antiretroviral Treatment (HAART)	
Leprosy (Hansen's Disease)		Prevention of HIV Infection	
Syphilis		Types of Testing	
Lyme Disease		HIV Pre- and Post-test Counselling	
Toxic Shock Syndrome (TSS)		<b>A Simplified Look at Antibiotics</b> .....	46
Cat Scratch Disease		<b>Antimicrobials</b> .....	47
Rocky Mountain Spotted Fever		Antibiotics	
West Nile Virus		<b>Antivirals</b> .....	51
<b>Fungal Infections</b> .....	28	<b>Antifungals</b> .....	53
Skin and Subcutaneous Infections		<b>Antiparasitics</b> .....	54
Superficial Fungal Infections		<b>Quick Reference: Common Infections and their Antibiotic Management</b> .....	55
Dermatophytes		<b>References</b> .....	56
Subcutaneous Fungal Infection			
Endemic Mycoses			
Opportunistic Fungi			
<i>Pneumocystis jiroveci</i> (formerly <i>P. carinii</i> )			
<i>Cryptococcus</i> spp.			

## Acronyms

AFB	acid-fast bacilli	ETEC	enterotoxigenic <i>E. coli</i>	HCV	hepatitis C virus	LP	lumbar puncture	Sn	sensitivity
AIDS	acquired immune deficiency syndrome	FDP	fibrinogen degradation products	HDV	hepatitis D virus	MDR	multi-drug resistance	Sp	specificity
ANC	absolute neutrophil count			HEV	hepatitis E virus	MMR	measles/mumps/rubella	spp.	species
AOM	acute otitis media	FUO	fever of unknown origin	HHV	human herpes virus	MRSA	methicillin-resistant <i>S. aureus</i>	SRI	severe respiratory illness
ARV	anti-retroviral	GAS	group A <i>Streptococcus</i>	Hib	<i>Haemophilus influenzae</i> b	MSM	men who have sex with men	STEC	Shiga toxin-producing <i>E. coli</i>
BAL	bronchoalveolar lavage	GBS	group B <i>Streptococcus</i>	HIV	human immunodeficiency virus	N/V	nausea and/or vomiting	STI	sexually transmitted infection
BCG	Bacille Calmette-Guérin	GC	gonococcus	HPF	high power field	O&P	ova and parasites	TB	tuberculosis
C&S	culture and sensitivity	GN	Gram negative bacilli	HRlg	human rabies immunoglobulin	PCR	polymerase chain reaction	Tlg	tetanus immune globulin
CFU	colony forming units	GNB	Gram negative bacilli	HSV	herpes simplex virus	PMN	polymorphonuclear leukocytes	TMP/SMX	trimethoprim-sulfamethoxazole
CMV	cytomegalovirus	GP	Gram positive	HUS	hemolytic uremic syndrome	PNS	peripheral nervous system	TNF	tumour necrosis factor
CNS	central nervous system	H. flu	<i>Haemophilus influenzae</i>	IE	infective endocarditis	PPD	purified protein derivative	TORCH	toxoplasmosis, other, rubella, cytomegalovirus, HSV
CSF	cerebrospinal fluid	HAART	highly active antiretroviral treatment	IFN	interferon	RSV	respiratory syncytial virus	TSS	toxic shock syndrome
CXR	chest X-ray	HAV	hepatitis A virus	Ig	immunoglobulin	RTI	respiratory tract infection	URT	upper respiratory tract infection
DEET	N,N-Diethyl-meta-toluamide	Hbc	HBV core antigen	INH	isoniazid	RT-PCR	reverse transcriptase	UTI	urinary tract infection
DM	diabetes mellitus	HBsAg	HBV surface antigen	IVDU	intravenous drug use	SARS	severe acute respiratory syndrome	VRE	vancomycin-resistant <i>Enterococcus</i>
DVT	deep vein thrombosis	HBV	hepatitis B virus	KOH	potassium hydroxide	SBP	systolic blood pressure	VZV	varicella-zoster virus
EBV	Epstein-Barr virus	HCC	hepatocellular carcinoma	KSHV	Kaposi's sarcoma-associated herpes virus	SIADH	syndrome of inappropriate antidiuretic hormone secretion	WBC	white blood cell
EHEC	enterohemorrhagic <i>E. coli</i>			LOC	level of consciousness				
EIEC	enteroinvasive <i>E. coli</i>								

## Principles of Microbiology

### Bacteriology

#### Bacteria Basics

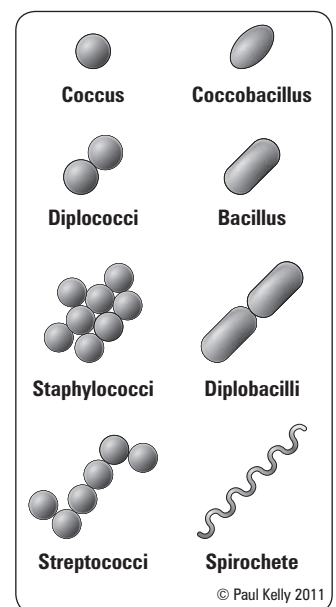
- bacteria are prokaryotic cells that divide asexually by binary fission
- chromosomal or plasmid DNA may be shared between bacteria through conjugation, transformation or transduction
- Gram stain divides most bacteria into two groups based on cell wall
  - Gram positive (GP): thick, rigid layer of peptidoglycan
  - Gram negative (GN): thin peptidoglycan layer + thicker outer membrane composed of lipoproteins and lipopolysaccharides
  - clinical significance: GN thick outer membrane makes it resistant to penicillin's attack
- acid-fast bacilli: "acid-fast" due to high mycolic acid content in cell wall, e.g. *Mycobacteria*, *Nocardia*
- "atypical" bacteria: not seen on Gram stain and difficult to culture
  - obligate intracellular bacteria: e.g. *Chlamydia*
  - bacteria lacking cell wall: e.g. *Mycoplasma*
  - spirochetes: e.g. *Treponema pallidum*
- O<sub>2</sub> can be either vital or detrimental to growth
  - obligate aerobes: require O<sub>2</sub>
  - obligate anaerobes: require environment without O<sub>2</sub>
  - facultative anaerobes: can survive in environments with or without O<sub>2</sub>

#### Mechanisms of Bacterial Disease

- adherence to and colonization of skin or mucous membranes
  - e.g. fimbriae (pili): microfilaments extending through the cell wall – like burrs sticking to your clothes, they attach to epithelial cells e.g. *E. coli* in the urinary tract
- invasion or crossing normal epithelial barriers
- evasion of host defense system through inhibition of:
  - phagocytic uptake: polysaccharide capsule (*S. pneumoniae*, *N. meningitidis*, *H. influenzae*) or surface proteins (*Staphylococcus*, *Streptococcus*)
- toxin production
  - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (e.g. *Clostridium*)
  - endotoxins are structural components of GN bacterial cell wall, and may be shed by live cells or released during cell lysis
- intracellular growth
  - obligate intracellular: *Rickettsia* and *Chlamydia*
  - facultative intracellular: *Salmonella*, *Neisseria*, *Brucella*, *Mycobacteria*, *Listeria*, *Legionella*
- biofilm
  - an extracellular polysaccharide network forming mesh around the bacteria (e.g. *S. epidermidis*) which can coat prosthetic devices like IV catheters



Gram positive bacteria have thick peptidoglycan layers.



© Paul Kelly 2011

Figure 1. Bacteria morphology

Table 1. Common Bacteria

Gram-positive Bacteria		Gram-negative Bacteria		Not Seen on Gram Stain	
Cocci	Bacilli (rods)	Diplococci	Bacilli (rods)	Acid Fast	Others
<b>Aerobes</b> <i>Staphylococcus</i> <i>S. aureus</i> <i>S. saprophyticus</i> <i>S. epidermidis</i> <i>Streptococcus</i> <i>S. pneumoniae</i> <i>S. pyogenes</i> (GAS) <i>S. agalactiae</i> (GBS) <i>Enterococcus</i> <i>E. faecalis</i>	<i>Bacillus</i> <i>B. anthracis</i> <i>Listeria</i> <i>Nocardia</i> (modified acid fast positive)	<i>Neisseria</i> <i>N. meningitidis</i> <i>N. gonorrhoeae</i> <i>Moraxella</i> <i>M. catarrhalis</i>	<i>Enterobacteriaceae</i> <i>E. coli</i> , <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i> <i>Klebsiella</i> <i>Legionella</i> <i>Pseudomonas</i> <i>Haemophilus</i> <i>H. influenzae</i>	<i>Mycobacteria</i> <i>M. tuberculosis</i> <i>M. leprae</i> <i>M. avium</i> complex <i>M. bovis</i>	Obligate intracellular <i>Rickettsiae</i> <i>Chlamydia</i> <i>C. trachomatis</i> <i>Chlamydia</i> <i>C. pneumoniae</i> No cell wall <i>Mycoplasma</i> Spirochaete (spiral) <i>Treponema pallidum</i>
<b>Anaerobes</b> <i>Peptostreptococcus</i>	<i>Clostridium</i> <i>C. difficile</i> , <i>C. tetani</i> , <i>C. botulinum</i> , <i>C. perfringens</i>		<i>Bacteroides</i> <i>B. fragilis</i>		

Table 2. Commensal Flora

Site	Organisms
<b>Skin</b>	Coagulase-negative staphylococci, <i>Corynebacteria</i> , <i>Propionibacterium acnes</i> , <i>Bacillus</i> , <i>S. aureus</i>
<b>Oropharynx</b>	Viridans group streptococci, <i>Haemophilus</i> , <i>Neisseria</i> , anaerobes ( <i>Peptostreptococcus</i> , <i>Bacteroides</i> , <i>Veillonella</i> , <i>Fusobacterium</i> , <i>Actinomyces</i> , <i>Prevotella</i> )
<b>Small bowel</b>	<i>E. coli</i> , anaerobes (low numbers)
<b>Colon</b>	<i>E. coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Enterococcus</i> , anaerobes ( <i>Bacteroides</i> , <i>Peptostreptococcus</i> , <i>Clostridium</i> )
<b>Vagina</b>	<i>Lactobacillus acidophilus</i> , Viridans group streptococci, coagulase-negative staphylococci, facultative GN bacilli, anaerobes

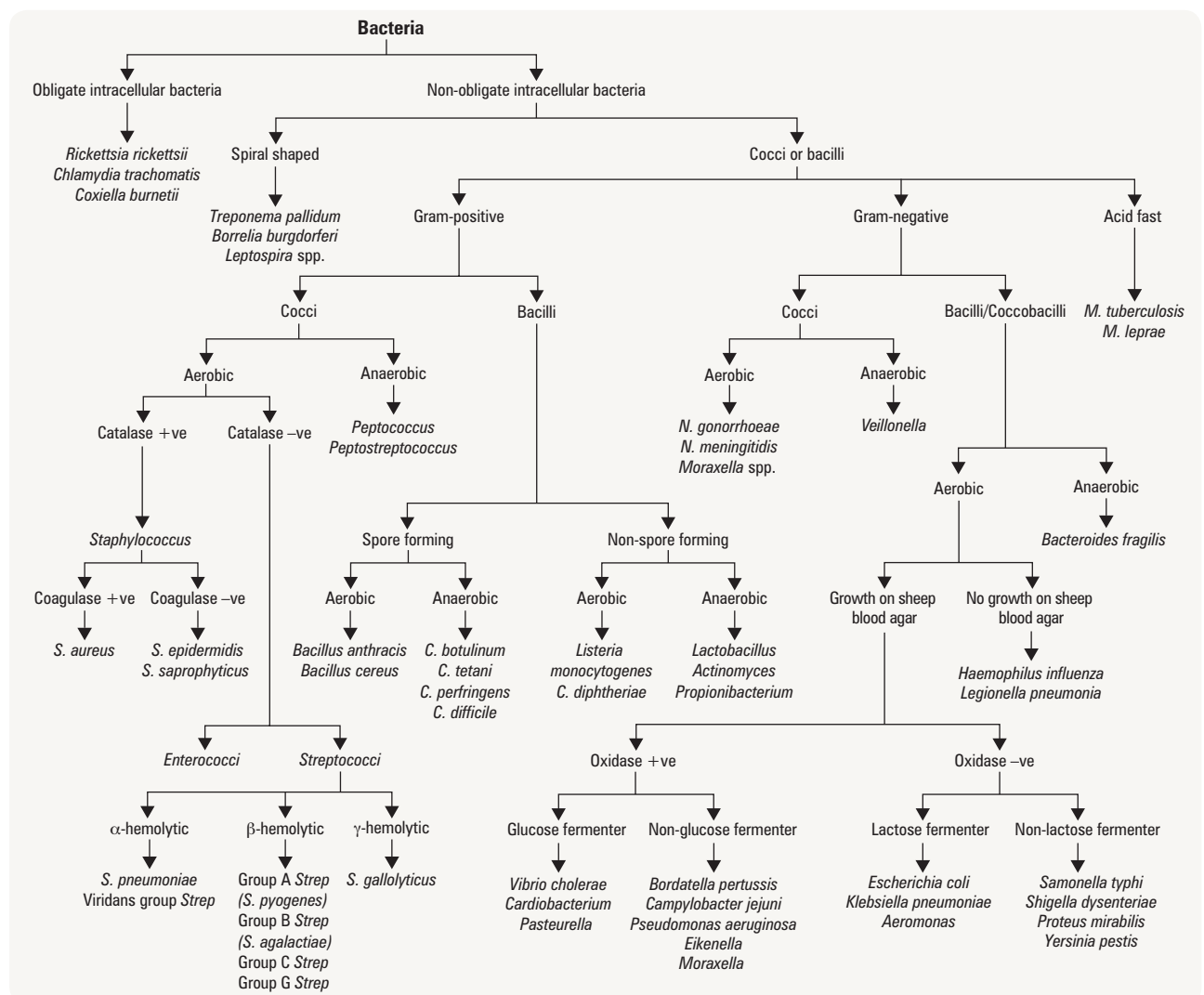


Figure 2. Laboratory identification of bacterial species

## Virology

### Viral Basics

- viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - infect cells and use host metabolic machinery to replicate
  - nucleic acid can be double stranded (ds) or single stranded (ss)
  - can be enveloped or naked
- virions are mature virus particles that can be released into the extracellular environment
- host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

### Viral Disease Patterns

- acute infections (e.g. adenovirus)
  - host cells are lysed in the process of virion release
  - some produce acute infections with late sequelae (e.g. measles virus → subacute sclerosing panencephalitis)
- chronic infections (>6 mo): (e.g. HBV, HIV)
  - host cell machinery is used to produce and chronically release virions
- latent infections
  - viral genome remains latent in host cell nucleus
  - can reactivate (e.g. HSV, VZV)

**Table 3. Common Viruses**

Nucleic Acid	Enveloped	Virus Family	Major Viruses	Medical Importance
dsDNA	N	<i>Adenoviridae</i>	Adenovirus	URTI Conjunctivitis Gastroenteritis
	N	<i>Papillomaviridae</i>	HPV1,4 HPV6,11 HPV16,18, etc.	Plantar warts Genital warts Cervical/anal dysplasia and cancer
	Y	<i>Herpesviridae</i>	HHV1=HSV1 HHV2=HSV2 HHV3=VZV HHV4=EBV HHV5=CMV HHV6* HHV8=KSHV	Oral, ocular and genital herpes; encephalitis Genital, oral and ocular herpes; encephalitis Chicken pox, shingles Mononucleosis, viral hepatitis Retinitis, pneumonitis, hepatitis, encephalitis Roseola Kaposi's sarcoma, multicentric Castleman's disease, body cavity lymphoma
	N	<i>Polyomaviridae</i>	JC virus	Progressive multifocal leukoencephalopathy
	Y	<i>Hepadnaviridae</i> <i>Poxviridae</i>	Hepatitis B Variola	Hepatitis Smallpox
ssDNA	N	<i>Parvoviridae</i>	Parvovirus B19	Erythema infectiosum (Fifth disease)
(+)ssRNA	N	<i>Caliciviridae</i>	Norwalk Hepatitis E	Gastroenteritis Acute hepatitis
	N	<i>Picomaviridae</i>	Poliovirus Echovirus Rhinovirus Coxsackie virus Hepatitis A	Poliomyelitis URTIs, viral meningitis URTIs Hand-foot-and-mouth, viral meningitis, myocarditis Acute hepatitis
	Y	<i>Coronaviridae</i>	Coronavirus	URTIs, SARS
	Y	<i>Flaviviridae</i>	Yellow Fever Dengue Fever Hepatitis C West Nile	Yellow fever Dengue fever Hepatitis Encephalitis, flaccid paralysis
	Y	<i>Togaviridae</i>	Rubella	Rubella (German measles)
	Y	<i>Retroviridae</i>	HIV HTLV-1	AIDS T-cell leukemia and lymphoma
	Y	<i>Arenaviridae</i>	Lassa Fever	Lassa fever
(-)ssRNA	Y	<i>Filoviridae</i>	Ebola, Marburg	Hemorrhagic fever
	Y	<i>Orthomyxoviridae</i>	Influenza A, B, C	Influenza
	Y	<i>Paramyxoviridae</i>	Measles Mumps Parainfluenza RSV	Measles Mumps URTIs, croup, bronchiolitis Bronchiolitis, pneumonia
	Y	<i>Rhabdoviridae</i>	Rabies	Rabies
	N	<i>Reoviridae</i>	Rotavirus	Gastroenteritis
dsRNA	N	<i>Reoviridae</i>	Rotavirus	Gastroenteritis

Note:     viridae = family,     virus = genus, # = species (e.g. Retroviridae HIV-2)

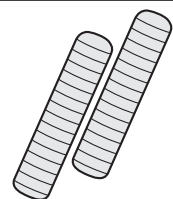
\*Roseolovirus, Herpes lymphotropic virus



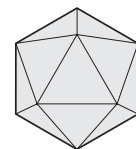
#### DNA Viruses: Families

##### HHAPPPy

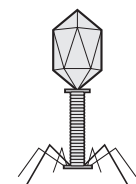
*Hepadnaviridae*  
*Herpesviridae*  
*Adenoviridae*  
*Papillomaviridae*  
*Polyomaviridae*  
*Parvoviridae*



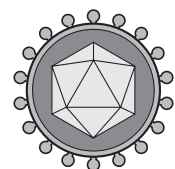
**Helical**



**Icosahedral**



**Complex**



**Enveloped**

© Beatrice Lau 2011

**Figure 3. Virus morphology**

## Mycology

### Fungal Basics

- fungi are eukaryotic organisms
  1. yeast (unicellular)
  2. molds (also known as filamentous fungi) (multicellular with hyphae)
  3. dimorphic fungi (found as mold at room temperature but grow as yeast-like forms at body temperature)

Table 4.

	Membrane Sterol	Cell wall
<b>Bacteria</b>	–	Peptidoglycan
<b>Human Cell</b>	Cholesterol	–
<b>Fungi</b>	Ergosterol	Chitin (complex glycopolysaccharide)

### Mechanisms of Fungal Disease

- primary fungal infection by:
  - overgrowth of normal flora (e.g. *Candida* species)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion aflatoxins)
- allergic reaction to fungi (e.g. bronchopulmonary aspergillosis)

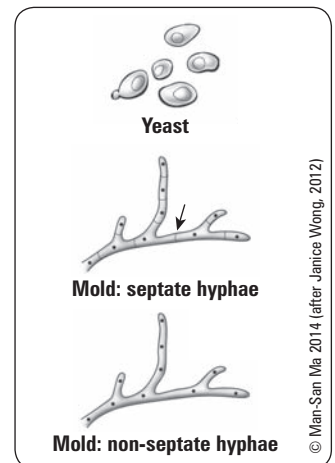


Figure 4. Common fungus morphology

## Parasitology

### Parasite Basics

- parasite: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycle requires more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed to the larval stage
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see Tables 21 and 22 for examples of clinically important parasites

Table 5. Differences Between Protozoa and Helminths

Protozoa	Helminths
Unicellular	Multicellular
Motile trophozoite → inactive cyst	Adult → egg → larva
Multiplication	No multiplication
± Eosinophilia	Eosinophilia (proportional to extent of tissue invasion)*
Indefinite life span	Definite life span

\*Adult ascaris (roundworm) does not cause eosinophilia

### Characteristics of Parasitic Disease

- spectrum of disease ranging from asymptomatic to severe illness
- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic infection

### Mechanisms of Parasitic Disease

1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B<sub>12</sub> deficiency in diphyllorhiosis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
  - acute hypersensitivity (e.g. pneumonitis in Loeffler's syndrome)
  - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
  - cytokine-mediated (systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
  - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
  - immune complex (e.g. nephritis of malaria, schistosomiasis)

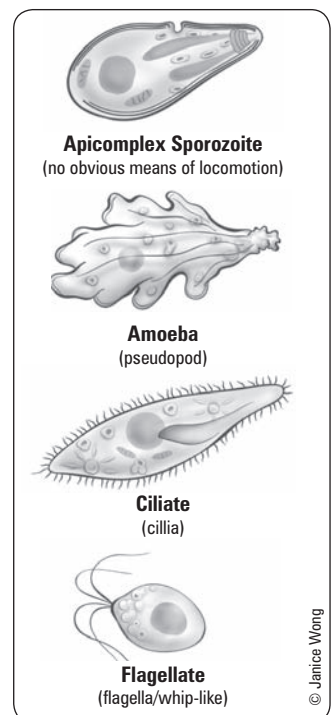


Figure 5. Classification of protozoa based on movement



Parasite sampling may need to be repeated on a number of occasions before infection can be ruled out.

## Transmission of Infectious Diseases

Table 6. Mechanism of Transmission

Mechanism	Mode of Transmission	Examples	Preventative Measure*
<b>Contact</b>	Direct physical contact, or indirect contact with a fomite.	Person-to-person (MRSA) Sexual ( <i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , HSV, HIV) Blood-borne (HIV, HBV, HCV)	For patients in health care facilities: Contact precautions (see <i>Prevention of Infectious Diseases</i> below) Barrier precautions Safe needlestick/sharp practices
<b>Droplet/Contact</b>	Respiratory droplets (>5 µm) can be projected short distances (≤2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids	Influenza, mumps <i>N. meningitidis</i> , <i>Bordetella pertussis</i>	For patients in health care facilities: Contact/droplet precautions (see <i>Prevention of Infectious Diseases</i> below)
<b>Airborne</b>	Airborne droplet nuclei (<5 µm) remain infectious over time and distance.	<i>M. tuberculosis</i> , VZV, measles	For patients in health care facilities: Airborne precautions (see <i>Prevention of Infectious Diseases</i> below)
<b>Food/Waterborne</b>	Ingestion of contaminated food or water	<i>V. cholerae</i> , <i>Salmonella</i> , HAV, HEV	Prophylactic vaccinations where available Ensure clean food/water supply For patients in health care facilities: Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers
<b>Zoonotic</b>	Disease transmission from animals to humans either directly or via an insect vector	Animals (rabies, Q fever) Arthropods (malaria, Lyme disease)	Prophylactic medications, vaccinations Protective clothing, insect repellent, mosquito nets, tick inspection
<b>Vertical</b>	Spread of disease from parent to offspring	Congenital syndromes (TORCH infections) Perinatal (HIV, HBV, GBS)	Prenatal screening Prophylactic treatment

\*see *Prevention of Infectious Diseases* for further detail

## Prevention of Infectious Diseases

### Overview

- efforts to control the spread of infectious disease involves **infection control and prevention measures** in health care settings and **public health measures** outside of health care settings

### Infection Control and Prevention Measures

- surveillance for important nosocomial infections or problem organisms (e.g. surgical site infections, vascular access-related infections, *C. difficile* infections, colonization or infections due to antimicrobial resistant organisms (e.g. methicillin-resistant *S. aureus*) (see [Population and Community Health](#), PH19 for a definition of active vs. passive surveillance)
- routine practices (also known as standard precautions) used for all patients
  - perform hand hygiene before and after seeing patient or patient environment contact, before aseptic procedures, and after body fluid exposure
  - use gloves for any encounter with body fluids
  - wear eye protection, mask, and gown for any procedures likely to generate splashes of body fluids
  - do not recap sharps by hand and dispose of sharps in puncture-resistant container near point-of-use
  - use mouthpieces for resuscitator bags instead of using mouth-to-mouth resuscitation
  - discard soiled waste properly
  - assure routine cleaning and disinfection of patient environment and patient care equipment
- additional precautions used for various syndromes or known infectious diseases
  - contact precautions (private room, gown, gloves to be used routinely) (e.g. used for patients with *C. difficile*)
  - droplet/contact precautions (private room, gown, gloves, eye protection, fluid-resistant mask) (e.g. used for influenza, meningitis due to *Neisseria meningitidis*)
  - airborne precautions (negative-pressure private room with door closed, fit-tested N95 respirator) (e.g. used for TB, measles, VZV)





- decolonization [e.g. topical and oral antimicrobials be used in an attempt to decolonize methicillin-resistant *S. aureus* (MRSA)]
- outbreak investigations (see [Population and Community Health](#), PH18)



### Public Health Measures

- vaccination
- post-exposure prophylaxis (e.g. use of immunoglobulin or vaccination post-exposure to infectious disease agents in an attempt to reduce the likelihood or severity of disease)
- reportable diseases (e.g. list of reportable communicable diseases that physicians are legally required to report to local public health officials) (see [Population and Community Health](#), PH25)
- contact tracing (tracking of individuals who have been exposed to a person with a communicable disease during its period of communicability)
- quarantine (restriction of the activities of well persons who have been exposed to a person with a communicable disease during its period of communicability to prevent disease transmission during the incubation period if infection should occur)
- outbreak investigation (see [Population and Community Health](#), PH18)



## Nosocomial Infections

- definition: infections acquired >48 h after admission to a health care facility or within 30 d from discharge
- risk factors: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
- patients with nosocomial infections have higher mortality, longer hospital stays, and higher health-care costs
- hand hygiene is an essential precaution

**Table 7. Common Nosocomial Infectious Agents**

Bacteria	Characteristics	Manifestation	Investigations	Management
<b>Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)</b>	Gram-positive cocci	Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis	Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR	Contact precautions For infection: vancomycin or daptomycin To decolonize: 2% chlorhexidine wash OD (+ rifampin + doxycycline + mupirocin cream bid to nares) x 7 d
<b>Vancomycin-resistant <i>Enterococcus</i> (VRE)</b>	Majority are <i>E. faecium</i> Resistant if minimum inhibitory concentration of vancomycin is $\geq 32$ $\mu\text{g/mL}$	Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis	Rectal or perirectal swab OR stool culture for colonization Culture of infected site	Contact precautions Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified
<b><i>Clostridium difficile</i> (C. difficile)</b>	Releases exotoxins A and B Hypervirulent strain has been responsible for increase in incidence and severity	Fever, nausea, abdo pain Watery diarrhea $\pm$ occult blood Pseudomembranous colitis Severe: toxic megacolon Risk of bowel perforation Associated with antibiotic use Leukocytosis	Stool PCR Stool immunoassay for toxins A and B AXR (may see colonic dilatation) Endoscopy (if suspect fulminant colitis)	Contact precautions Stop culprit antibiotic therapy Supportive therapy (IV fluids) Mild-moderate disease: metronidazole PO/IV x 10-14 d Severe disease: vancomycin PO x 10-14 d Toxic megacolon: metronidazole IV + vancomycin PO (as above) and general surgery consult
<b>Extended spectrum <math>\beta</math>-lactamases (ESBL e.g. <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>)</b>	Resistant to most $\beta$ -lactam producing antibiotics e.g. penicillins, aztreonam and cephalosporins	UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis	Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)	Droplet or contact precautions depending on site of infection and institutional policies Depending on culture and sensitivity results, carbapenems can be used for empiric therapy

# Respiratory Infections



## Pneumonia

- see [Pediatrics](#), P93
- see [Family Medicine](#), FM18

### Definition

- infection of the lung parenchyma

### Etiology and Risk Factors

- impaired lung defenses
  - poor cough/gag reflex (e.g. illness, drug-induced)
  - impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  - immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
- increased risk of aspiration
  - impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia, mechanical obstruction)
- no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

**Table 8. Common Organisms in Pneumonia**

Community Acquired	Nosocomial	Aspiration	HIV-associated	Alcoholic
Typical Bacteria <i>Streptococcus pneumoniae</i> <i>Moraxella catarrhalis</i> <i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i> GAS	Enteric GNB ( <i>E. coli</i> ) <i>Pseudomonas aeruginosa</i> <i>S. aureus</i> (including MRSA)	Oral anaerobes ( <i>Bacteroides</i> ) Enteric GNB ( <i>E. coli</i> ) <i>S. aureus</i> Gastric contents (chemical pneumonitis)	<i>Pneumocystis jirovecii</i> Fungi ( <i>Cryptococcus</i> ) <i>Nocardia</i> CMV HSV TB	<i>Klebsiella</i> Enteric GNB <i>S. aureus</i> Oral anaerobes (aspiration) TB
Atypical Bacteria <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> <i>Legionella pneumophila</i>				
Viral Influenza virus Adenovirus				

\*See [Pediatrics](#) P93, Table 45 for Common Causes and Treatment of Pneumonia at Different Ages

### Clinical Features

- cough ( $\pm$  sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
- elderly often present atypically; altered LOC is sometimes the only sign
- evidence of consolidation (dullness to percussion, bronchial breath sounds, crackles, increased fremitus, whisper pectoriloquy)
- features of parapneumonic effusion (decreased air entry, dullness to percussion, decreased fremitus) (see [Respirology](#), R21)
- complications: ARDS, lung abscess, parapneumonic effusion/empyema, pleuritis  $\pm$  hemorrhage

### Investigations

- pulse oximetry to assess severity of respiratory distress
- CBC and differential, electrolytes, urea, Cr, ABG (if respiratory distress), troponin/CK, LFTs, urinalysis
- sputum Gram stain/C&S, blood C&S,  $\pm$  serology/viral detection,  $\pm$  pleural fluid C&S (if effusion >5 cm or respiratory distress)
- CXR $\pm$ CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate  $\pm$  cavitation
- bronchoscopy  $\pm$  washings for
  - (1) severely ill patients refractory to treatment or (2) immunocompromised patients

### Treatment

- ABC, O<sub>2</sub>, IV fluids, consider salbutamol (nebulized or MDI)
- determine prognosis and need for hospitalization and antibiotics



When *Klebsiella* causes pneumonia; see red currant jelly.



#### 3 As of *Klebsiella*

Aspiration pneumonia  
Alcoholics and diabetics  
Abscess in lungs



Aspiration pneumonias more commonly manifest as infiltrates in the right middle or lower lobes due to the larger caliber and more vertical orientation of the right bronchus.



Lobar Pneumonia



Bronchopneumonia



Interstitial Pneumonia

©Stuart Jantzen 2012

**Figure 6. Lobar, broncho and interstitial pneumonia**

## Criteria for Hospitalization

**Table 9. CURB 65 Score – Pneumonia Clinical Prediction Tool**

Component	Measurement(s)	Points	Total Score	Mortality	Disposition
Confusion	Altered mental status	1	0-1	<5%	Can treat as outpatient
Urea/BUN	Urea >7 mmol or BUN >19	1	2-3	5-15%	Consider hospitalization
Respiratory Rate	>30 breaths/min	1	4-5	15-30%	Consider ICU
Blood Pressure	Systolic <90 or diastolic <60 mmHg	1			
Age	65 or older	1			

**Table 10. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007**

Setting	Circumstances	Treatment
Outpatient	Previously well No antibiotic use in last 3 mo	Macrolide <sup>1</sup> OR Doxycycline
	Comorbidities <sup>2</sup> Antibiotic use in last 3 mo (use different class)	Respiratory fluoroquinolone <sup>3</sup> OR $\beta$ -lactam <sup>4</sup> + Macrolide <sup>1</sup>
Inpatient	Ward	Respiratory fluoroquinolone <sup>3</sup> OR $\beta$ -lactam <sup>4</sup> + Macrolide <sup>1</sup>
	ICU	$\beta$ -lactam <sup>4</sup> + [Macrolide <sup>1</sup> OR Respiratory fluoroquinolone <sup>3</sup> ]

1. **Macrolide:** azithromycin, clarithromycin, erythromycin

2. **Comorbidities:** chronic heart, lung, liver or renal disease, DM, alcoholism, malignancy, asplenia, immunocompromised

3. **Respiratory fluoroquinolone:** moxifloxacin, gemifloxacin, levofloxacin

4.  **$\beta$ -lactam:** cefotaxime, ceftriaxone, ampicillin-sulbactam

IDSA: Infectious Diseases Society of America

ATS: American Thoracics Society

**Table 11. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005**

Setting	Treatment
No risk factors for multi-drug resistance (MDR) Early onset (<5 d)	ceftriaxone OR levofloxacin, moxifloxacin, or ciprofloxacin OR ampicillin/sulbactam OR ertapenem
Late onset disease ( $\geq 5$ d) or With risk factors for MDR: Antibiotic use in last 3 mo High frequency of antibiotic resistance in the community or in the specific hospital unit Hospitalization >1 d in past 3 mo Residence in a nursing home or extended care facility Dialysis within 30 d Home wound care Family member with multidrug-resistant pathogen Immunosuppressive disease and/or therapy	antipseudomonal cephalosporin (cefepime or ceftazidime) OR antipseudomonal carbapenem (imipenem or meropenem) OR $\beta$ -lactam/ $\beta$ -lactamase inhibitor (piperacillin/tazobactam) PLUS antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR aminoglycoside (amikacin, gentamicin, or tobramycin) PLUS for MRSA linezolid or vancomycin PLUS for <i>Legionella</i> ensure regime includes either a macrolide or a fluoroquinolone

Note: Always use directed therapy against specific organism if one is found on culture (e.g. blood, sputum, etc.)

Note: These guidelines may be less applicable in Canada given lower rates of antibiotic resistance among common nosocomial pathogens



### Does this Adult Patient have Pneumonia?

#### From The Rational Clinical Examination

JAMA 2009; http://www.jamaevidence.com/content/3485708

**Study:** Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult community acquired pneumonia.

**Results:** The presence of fever or Immunosuppression had a positive likelihood ratio (+LR) of 2, while a history of dementia had a +LR of 3; however, these traits are not confirmatory. The presence of an abnormality in any vital sign, including tachycardia, tachypnea or fever had a +LR ranging from 2-4, which was not significantly affected by different cut-points. The absence of vital sign abnormality had a -LR ranging from 0.5-0.8. The combination of respiratory rate <30/min, heart rate <100/min and temperature <37.8°C had a -LR of 0.18. Findings on chest exam raised the likelihood of diagnosis, but were uncommonly seen in studies. For example, presence of asymmetric respirations essentially confirmed the diagnosis, but was only present in 4% of patients. In patients with a clinical diagnosis, but normal radiograph, only ~10% will develop radiographic findings in 72 h.

**Conclusions:** Evidence suggests no single item on clinical history or physical exam is sufficient to rule in or out pneumonia without chest x-ray. Vital sign abnormalities were correlated with a diagnosis of pneumonia. Findings on chest exam significantly raised the likelihood of pneumonia, but were uncommonly seen in studies.

## Prevention

- Public Health Agency of Canada recommends the following:

- vaccine for influenza A and B recommended annually for all ages
- pneumococcal polysaccharide vaccine (Pneumovax®) recommended for all adults >65 yr and in younger patients 24 mo of age and older at high risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia; congenital or acquired immunodeficiency)
- pneumococcal conjugate vaccine (Prevnar-13®) is recommended for all children <5 yr, and for children and adolescents at high risk for invasive pneumococcal disease who are 5-17 yr who have not previously received Prevnar-13® (CDC recommends giving Prevnar-13® to all adults at high risk for invasive pneumococcal disease)

## Influenza

### Definitions and Etiology

- influenza virus A and B
- influenza A further divided into subtypes based on envelope glycoproteins:
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: human-origin A (H1N1) and B (H3N2) subtypes
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift (abrupt, major changes due to mixing of two different viral strains from different hosts)
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

**Table 12. Difference between Influenza Strains**

	Influenza A	Influenza B
Host(s)	Humans, Birds, Mammals	Humans only
Antigenic drift	Yes, new strains	Yes, new strains
Antigenic shift	Yes, new subtypes	No
Epidemics	Yes	Yes
Pandemics	Yes	No

### Clinical Features

- incubation period 1-4 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, headache, fatigue) and respiratory symptoms (cough, dyspnea, pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, Guillain-Barré syndrome)

### Investigations

- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for rapid antigen detection, DFA (Direct Fluorescent Antigen detection), RT-PCR (gold standard)
- serology: rarely used for clinical management

### Treatment and Prevention

- primarily supportive unless severe infection or high-risk of complications (e.g. elderly, pulmonary or cardiac disease)
- neuraminidase inhibitors: zanamivir (Relenza®) and oseltamivir (Tamiflu®) for treatment and prophylaxis against type A and B
  - decreases duration (by 1-2 d) and severity of symptoms if given within <48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- M2-inhibitors: amantidine/rimantidine for treatment and prophylaxis against type A only no longer recommended due to increased resistance
- vaccine for influenza A and B viruses is recommended annually for all ages
  - vaccine is reformulated each year to reflect circulating influenza A and B strains



**Beware! Do not confuse *H. influenzae* with influenza virus**

*H. influenzae*: a bacterium (Types A, B, C, D, E, F, refer to capsule)

Influenza: a virus (Types A and B refer to strain)



**Vaccines for Preventing Influenza in Healthy Adults**

*Cochrane DB Syst Rev* 2010;CD001269

**Study:** Meta-analysis of RCTs and quasi-RCTs evaluating influenza vaccines compared to placebo in healthy individuals aged 16 to 65 yr.

**Results:** 50 reports were included. If vaccine matched the viral circulating strain, 4% of unvaccinated people versus 1% of vaccinated people developed influenza symptoms; the corresponding figures for poor vaccine matching were 2% and 1%. Vaccination had a modest effect on time off work and had no effect on hospital admissions or complication rates. Inactivated vaccines caused local harms and 1.6 additional cases of Guillain-Barré Syndrome per million vaccinations.

**Conclusions:** Vaccination has a modest effect in reducing influenza symptoms and time off work.

## Skin and Soft Tissue Infections

### Cellulitis

#### Definition

- acute infection of the skin principally involving the dermis and subcutaneous tissue

#### Etiology

- common causative agents: *S. aureus*,  $\beta$ -hemolytic streptococci
- immunocompromised patients: may also include GN rods and fungi
- risk factors:
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema diabetes, cracked skin in feet/toes (tinea pedis)

**Clinical Features**

- pain, tenderness, edema, erythema with indistinct borders  $\pm$  regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
- can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

**Investigations**

- CBC and differential, blood C&S if febrile
- skin swab ONLY if open wound with pus

**Treatment**

- antibiotics: cephalexin
- if extensive erythema or systemic symptoms, consider cefazolin IV
- limb rest and elevation may help reduce swelling

## Necrotizing Fasciitis

**Definition**

- life- and limb-threatening infection of the deep fascia characterized by rapid spread

**Etiology**

- Two main forms:
  - Type I: polymicrobial infection – aerobes and anaerobes (e.g. *S. aureus*, *Bacteroides*, *Enterobacteriaceae*)
  - Type II: monomicrobial infection with GAS

**Clinical Features**

- pain out of proportion to clinical findings and beyond border of erythema
- edema,  $\pm$  crepitus (subcutaneous gas from anaerobes),  $\pm$  fever
- infection spreads rapidly
- patients may rapidly become very sick (tachycardia, hypotension, lightheadedness)
- late findings:
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of hemorrhagic bullae

**Investigations**

- a clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
- blood and tissue C&S
- serum CK (elevated CK usually means myonecrosis – a late sign)
- plain film x-ray (soft tissue gas may be visualized)
- surgical exploration for debridement of infected tissue

**Treatment**

- resuscitation with IV fluids
- emergency surgical debridements to confirm diagnosis and remove necrotic tissue
- IV antibiotics
  - unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV  $\pm$  vancomycin if MRSA is considered
  - Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  - Type II (monomicrobial): penicillin G + clindamycin IV
  - with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIG

## Gastrointestinal Infections

### Acute Diarrhea

- see [Gastroenterology](#), G15
- see [Pediatrics](#), P35
- see [Family Medicine](#), FM26

**Epidemiology**

- one of five leading causes of death worldwide, according to World Health Organization
- significant morbidity in developed countries (over 900,000 hospitalizations in United States each year)

## Definition

- passage of  $\geq 3$  loose or liquid stools/d or  $>200$  g stool/d for  $>2$  d but  $\leq 14$  d

## Approach to Acute Diarrhea

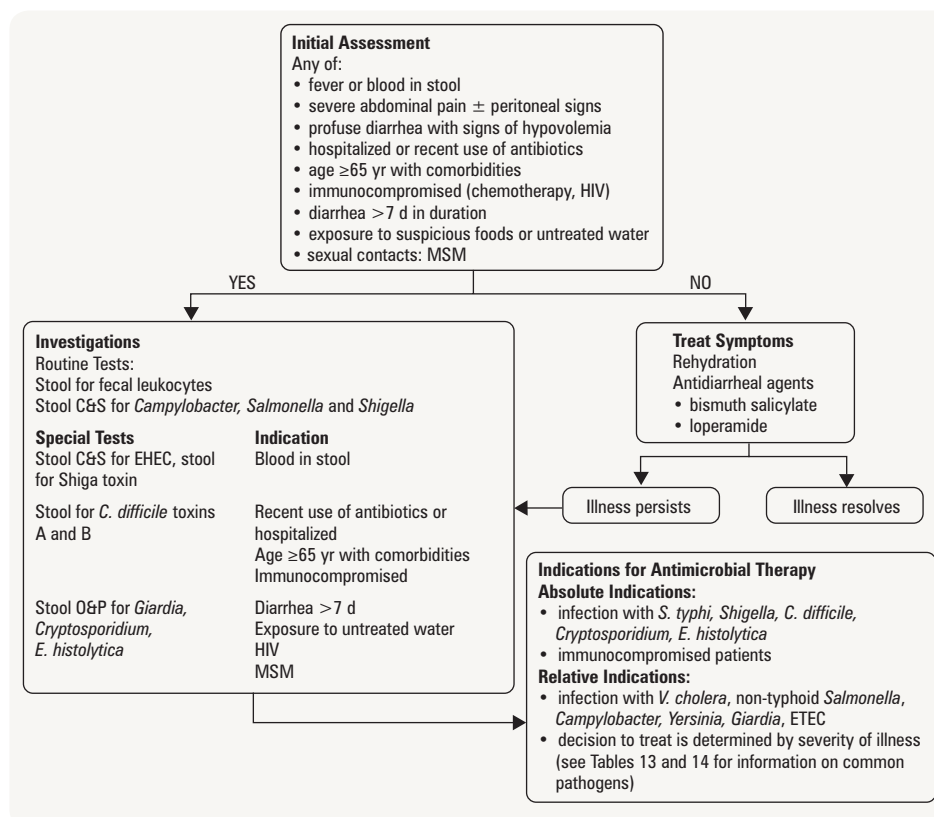
- rationale:
  - the vast majority of acute diarrhea is caused by infection
  - in most cases, acute diarrheal illness is viral and/or self-limited, and lasts  $<3$  d
  - investigations are costly and are necessary only in certain circumstances
- therefore, the evaluation of acute diarrhea involves:
  - identifying characteristics of the illness or patient that warrant further investigation
  - assessing volume status to determine appropriate method of rehydration
- see Figure 7

## Physical Exam

- volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
- abdominal exam: pain, guarding, peritoneal signs

## Treatment

- rehydration is mainstay of treatment
  - oral rehydration therapy
  - IV rehydration if oral intake insufficient to replace fluid loss
- antidiarrheal agents reduce duration of diarrhea: loperamide, bismuth salicylate
  - delays excretion of causative pathogens
  - contraindications: diarrhea with fever, bloody stool or diarrhea caused by *Clostridium difficile*
- antibiotic therapy is rarely indicated because:
  - most acute diarrheal illness is of viral etiology and is self-limited
  - antibiotics can eradicate normal gut flora, predisposing to *C. difficile* infection
  - antibiotics prolong the shedding of *Salmonella* and other causes of bacterial diarrhea
  - in EHEC infection, antibiotics may increase the risk of HUS
  - indications for antibiotic therapy are shown in Figure 7



### Causes of Acute Bloody Diarrhea

#### CHESS

*Campylobacter*  
Hemorrhagic *E. coli* (e.g. O157:H7)  
*Entamoeba histolytica*  
*Salmonella*  
*Shigella*

Figure 7. Approach to acute diarrhea



Table 13. Bacteria in Infectious Diarrhea

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	N/V			
<i>B. cereus</i> – Type A (emetic)	Rice dishes	1-6 h	–	–	–	+	<12 h	None	Preformed exotoxin
<i>B. cereus</i> – Type B (diarrheal)	Meats, vegetables, dried beans, cereals	8-16 h	–	–	–	–	<24 h	None	Secondary endotoxin
<i>Campylobacter jejuni</i>	Uncooked meat, especially poultry	2-10 d	+	±	+	±	<1 wk	Macrolide or fluoroquinolone if diarrhea >1 wk, bloody diarrhea, or immunocompromised	Most common bacterial cause of diarrhea in Canada Associated with Guillain-Barré syndrome
<i>Clostridium difficile</i>	Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antimicrobials)	Unclear	±	±	±	–	Variable	Discontinue offending antimicrobial agent, if possible 1st line – metronidazole (PO/IV) or vancomycin PO in severe cases 2nd line – vancomycin PO	Usually follows antibiotic treatment (especially clindamycin, fluoroquinolones, penicillins, cephalosporins) Can develop pseudomembranous colitis
<i>Clostridium perfringens</i>	Contaminated food, especially meat and poultry	8-12 h	±	–	+	–	<24 h	None	<i>Clostridium</i> spores are heat resistant Secondary enterotoxin
Enteroinvasive <i>E. coli</i> (EIEC)	Contaminated food/water	1-3 d	+	±	+	–	7-10 d	None	Relatively uncommon
Enterotoxigenic <i>E. coli</i> (ETEC)	Contaminated food/water	1-3 d	–	–	+	–	3 d	Fluoroquinolone or azithromycin for moderate to severe symptoms	Most common cause of traveller's diarrhea Heat-labile and heat-stable toxins
Enterohemorrhagic <i>E. coli</i> (EHEC/STEC) i.e. O157:H7	Contamination of hamburger, raw milk, drinking and recreational water	3-8 d	–	+	+	±	5-10 d	None: antibiotics increase risk of HUS	Shiga toxin production Monitor renal function: 10% develop HUS Antidiarrheals increase risk of HUS
<i>Salmonella typhi</i> <i>S. paratyphi</i> (aka Enteric Fever, Typhoid)	Fecal-oral Contaminated food/water, travel to endemic area	10-14 d	+	±	+	±	<5-7 d	Empiric treatment with ceftriaxone or azithromycin Fluoroquinolone resistance is increasing	<i>Salmonella typhi</i> : "Rose spot" rash (on anterior thorax, upper abdomen), fever and abdominal pain precedes diarrhea
Non-typhoidal Salmonellosis <i>S. typhimurium</i> , <i>S. enteritidis</i>	Contaminated animal food products, especially eggs, poultry, meat, milk	12-72 h	+	±	+	+	3-7 d	Ciprofloxacin only in severe illness, extremes of age, joint prostheses, valvular heart disease, severe atherosclerosis, cancer, uremia	
<i>Shigella dysenteriae</i>	Fecal-oral Contaminated food/water	1-4 d	+	±	+	+	<1 wk	Fluoroquinolone	Very small inoculum needed for infection Complications include toxic megacolon, HUS Antidiarrheals may increase risk of toxic megacolon
<i>Staphylococcus aureus</i>	Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)	2-4 h	–	–	+	+	1-2 d	None	Heat-stable preformed exotoxin
<i>Vibrio cholerae</i>	Contaminated food/water, especially shellfish	1-3 d	–	–	–	–	3-7 d	Tetracycline or quinolones (ciprofloxacin)	Massive watery diarrhea (1-3 L/d) Mortality <1% with treatment
<i>Yersinia</i>	Contaminated food Unpasteurized milk	5 d	+	±	+	±	Up to 3 wk	Fluoroquinolone only for severe illness	Majority of cases in children 1-4 yr Mesenteric adenitis and terminal ileitis can occur without diarrhea, mimicking appendicitis

**Table 14. Parasites in Infectious Diarrhea**

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	N/V			
<i>Cryptosporidium</i>	Fecal-oral	7 d	±	–	–	+	1-20 d	Paramomycin + nitazoxanide	
<i>Entamoeba histolytica</i>	Worldwide endemic areas Fecal-oral	2-4 wk	±	+	–	+	Variable	Metronidazole + iodoquinol if symptomatic infection Only iodoquinol for asymptomatic cyst passage	If untreated, potential for liver abscess Sigmoidoscopy shows flat ulcers with yellow exudates
<i>Giardia lamblia</i>	Fecal-oral Contaminated food/water	1-4 wk	–	–	+	+	Variable	Metronidazole or nitazoxanide Treatment of asymptomatic carriers not recommended	Higher risk in: day care children, intake of untreated water ("beaver fever"), MSM, immunodeficiency (decreased IgA) May need duodenal biopsy

**Table 15. Viruses in Infectious Diarrhea**

Pathogen	Source or Mode of Transmission	Incubation	Clinical Features				Duration	Antimicrobial Therapy	Notes
			Fever	Bloody Stool	Abdo Pain	N/V			
Norovirus	Fecal-oral	24 h	–	–	+	+	24 h	None	Noroviruses includes Norwalk virus
Rotavirus	Fecal-oral	2-4 d	±	–	–	±	3-8 d	None	Can cause severe dehydration Virtually all children are infected by 3 yr of age Oral vaccine given at 2 and 4 mo of age

## Traveller's Diarrhea

- see *Acute Diarrhea*, ID11

### Epidemiology

- the most common illness to affect travellers
- up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

### Etiology

- bacterial (80-90%): *E. coli* most common (ETEC), *Campylobacter*, *Shigella*, *Salmonella*, *Vibrio* (non-cholera); wide regional variation (e.g. *Campylobacter* more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): *Giardia*, *Entamoeba histolytica*, *Cryptosporidium*, *Cyclospora* for ~10% in long-term travellers
- pathogen-negative traveller's diarrhea common despite exhaustive microbiological work-up

### Treatment

- rehydration is mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss use oral rehydration solutions (1 package in 1L boiled or treated water)
- treat symptoms: antidiarrheal agents (e.g. bismuth salicylate, loperamide)
- empiric antibiotics in moderate or severe illness: ciprofloxacin or azithromycin or rifaximin
  - note: there is increasing fluoroquinolone resistance in causative agents, especially in Southeast Asia



Bismuth salicylate (Pepto-Bismol®) can cause patients to have black stools, which may be mistaken for melena.

### Prevention

- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
- bismuth salicylate (Pepto-Bismol®): 60% effective (2 tablets qid according to CDC website)
- CDC Guideline: antibiotic prophylaxis not recommended
  - increased risk of infection with resistant organisms
  - high risk groups (e.g. immunocompromised) likely to be infected with pathogen not covered by standard antimicrobial agents

- Dukoral®: oral vaccine that offers protection against *V. cholera* (efficacy ~80%) and ETEC (efficacy ~50-67%). Not recommended for routine use in travellers, but PHAC recommends that it may be considered in short-term travellers >2 yr who are high-risk (e.g. chronic illness) for whom there is an increased risk of serious consequences for traveller's diarrhea (e.g. chronic renal failure, congestive heart failure, type 1 diabetes mellitus, inflammatory bowel disease), immunosuppressed, history of repeat traveller's diarrhea, increased risk of acquiring traveller's diarrhea (gastric hypochlorhydria or young children >2 yr)

## Chronic Diarrhea

- see [Gastroenterology](#), G16



## Peptic Ulcer Disease (*H. pylori*)

- see [Gastroenterology](#), G12



# Bone and Joint Infections

## Septic Arthritis

### Routes of Infection

- hematogenous (adults)
- contiguous osteomyelitis (children)
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

### Etiology

- gonococcal
  - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* species (Group A and B)
  - Gram-negatives: affects neonates, elderly, IV drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae*: affects children aged <2 yr since Hib immunization
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* species: prosthetic joints
- if culture negative: *Borrelia* spp. (Lyme disease) or *Tropheryma whippelii* (Whipple's disease)

### Risk Factors

- gonococcal
  - age (<40 yr old), recent menses, pregnancy, MSM
- non-gonococcal
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (rheumatoid arthritis, osteoarthritis)
  - immunocompromise (diabetes, chronic kidney disease, alcoholism, cirrhosis)
  - loss of skin integrity (cutaneous ulcer, skin infection)
  - age >80 yr

### Clinical Features of Gonococcal Arthritis

- two forms (although overlap often):
  - bacteremic form:
    - ♦ systemic symptoms: fever, malaise, chills
    - ♦ gonococcal triad: migratory polyarthralgias, tenosynovitis, dermatitis (pustular skin lesions)
  - septic arthritis form:
    - ♦ local symptoms in involved joint: swelling, warmth, pain, inability to bear weight, marked decreased in range of motion (see [Rheumatology](#), RH3 for differential diagnosis)



#### Medical Emergency

Septic arthritis is a medical emergency! If untreated, rapid joint destruction will occur.



#### Gonococcal Triad

- Migratory arthralgias
- Tenosynovitis next to inflamed joint
- Pustular skin lesions

### Clinical Features of Non-gonococcal Arthritis

- acute onset of pain, swelling, warmth, decreased range of motion ± fever, chills
- most often in large weight bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)



### Investigations

- consider rheumatologic causes for monoarthritis (see [Rheumatology](#), RH3)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBC count ( $>15\,000/\text{mm}^3$ : likelihood of infection increases with increasing WBC count), PMNs  $>90\%$ , culture positive
  - growth of *N. gonorrhoeae* from synovial fluid is successful in  $<50\%$  of cases
- $\pm$  plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment

### Treatment

- medical
  - empiric IV antibiotics (vancomycin + ceftriaxone) – delay may result in joint destruction
  - Gram stain guides subsequent treatment
  - gonococcal: ceftriaxone + azithromycin, for concurrent treatment of *C. trachomatis*
  - non-gonococcal: antibiotics against *Streptococcus* spp. (2 wk), *S. aureus* (4 wk IV minimum), or GN rods (4 wk)
- surgical drainage if: (see [Orthopedics](#), OR10)
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement
  - prosthetic joint
- daily joint aspirations until culture sterile; no need to give intra-articular antibiotics
- physiotherapy

### Prognosis

- gonococcal: responds well after 24–48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: up to 50% morbidity (decreased joint function/mobility)



Intra-articular steroids are contraindicated until septic arthritis has been excluded.

## Diabetic Foot Infections

### Etiology

- neuropathy, peripheral vascular disease and hyperglycemia contribute to foot ulcers that heal poorly and are predisposed to infection
- organisms in mild infection: *S. aureus*, *Streptococcus* spp.
- organisms in moderate/severe infection: polymicrobial with aerobes (*S. aureus*, *Streptococcus*, *Enterococcus*, GN bacilli) and anaerobes (*Peptostreptococcus*, *Bacteroides*, *Clostridium*)

### Clinical Features

- not all ulcers are infected
- diagnosis of infected ulcer:  $\geq 2$  of the cardinal signs of inflammation (redness, warmth, swelling, pain) or the presence of pus
- $\pm$  crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone = osteomyelitis
- infection severity:
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint)
  - severe = infection in a patient with systemic toxicity (fevers, chills, tachycardia, hypotension)

### Investigations

- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infection)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages)
  - if initial x-ray normal, repeat 2–4 wk after initiating treatment to increase test sensitivity
  - if initial x-ray equivocal, do MRI or bone biopsy (most reliable test)

### Treatment

- evaluate for early surgical debridement  $\pm$  revascularization or amputation
- eliminate/reduce pressure and provide regular local wound care
- mild: cephalexin or clindamycin
- moderate or severe: clindamycin + ciprofloxacin PO or pip/tazo IV  $\pm$  vancomycin if MRSA known or suspected
- encourage glycemic control



#### Does This Patient with Diabetes Have Osteomyelitis of the Lower Extremity?

JAMA 2008;299:806–813

**Study:** Systematic literature review. 21 studies.

**Population:** 1027 adult patients with diabetes mellitus being investigated for osteomyelitis.

**Intervention:** Various aspects of history, physical exam, laboratory tests, and diagnostic imaging studies versus bone biopsy.

**Primary outcome:** Diagnostic utility.

**Results:** No studies examined any part of history taking. Temperature, ulcer characteristics (erythema, swelling, purulence), elevated WBC, skin swabs, and soft tissue cultures were not useful. Nuclear imaging has poor specificity for osteomyelitis (62%–88.5%), and MRIs have greater accuracy in detecting osteomyelitis.

Finding	(+) LR	(–) LR
Visualization of bone	9.2	0.70
Ulcer area $>2\text{ cm}^2$	7.2	0.48
Probe-to-bone	6.4	0.39
Clinical judgment	5.5	0.54
ESR $>70\text{ mm/h}$	11	NS*
Plain radiographs	2.3	0.63
MRI	3.8	0.14

\*NS = not significant

## Osteomyelitis

- see [Orthopedics](#), OR10



# Cardiac Infections

## Infective Endocarditis (IE)



### Definition

- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
- leaflet vegetation = platelet-fibrin thrombi, WBCs and bacteria

### Risk Factors and Etiology

- predisposing conditions:
  - high risk: prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 mo, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - moderate risk: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - low/no risk: secundum ASD or surgically repaired ASD < VSD, PDA, MV prolapse, IHD, previous CABG
  - opportunity for bacteremia: intravenous drug use (IVDU), indwelling venous catheter, hemodialysis, poor dentition, diabetes, HIV
- frequency of valve involvement MV >> AV > TV > PV
  - but in 50% of IVDU-related IE the tricuspid valve is involved



MV mitral valve  
AV aortic valve  
TV tricuspid valve  
PV pulmonic valve



### Etiology of Culture-negative Endocarditis

- HACEK (fastidious Gram-negative bacilli)**

*Haemophilus parainfluenzae*  
*Aggregatibacter aphrophilus*/  
*Aggregatibacter*  
*actinomycetemcomitans*  
*Cardiobacterium hominis*  
*Eikenella corrodens*  
*Kingella kingae*

- Coxiella burnetii*
- Bartonella species*
- Tropheryma whippelii*
- Fungi
- Mycobacteria

**Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors**

Native Valve	IVDU	Prosthetic Valve (recent surgery <2 months)	Prosthetic Valve (remote surgery >2 months)
<b><i>Streptococcus</i><sup>1</sup> (36%)</b>	<b><i>S. aureus</i> (68%)</b>	<b><i>S. aureus</i> (36%)</b>	<b><i>Streptococcus</i> (20%)</b>
<b><i>S. aureus</i><sup>4</sup> (28%)</b>	<b><i>Streptococcus</i> (13%)</b>	<b><i>S. epidermidis</i> (17%)</b>	<b><i>S. aureus</i> (20%)</b>
<b><i>Enterococcus</i> (11%)</b>	<i>Enterococcus</i>	Other	<b><i>S. epidermidis</i> (20%)</b>
<i>S. epidermidis</i>	GNB	<i>Enterococcus</i>	<b><i>Enterococcus</i> (13%)</b>
GNB	<i>Candida</i>	GNB	Other <sup>2</sup>
Other <sup>2</sup>	Other <sup>3</sup>	Other <sup>2</sup>	

Organisms in bold are the most common isolates.

1. *Streptococcus* includes mainly Viridans group *streptococci*

2. Other includes less common organisms such as:

- Streptococcus bovis* (usually associated with underlying GI malignancy, cirrhosis)
- Culture-negative organisms including nutritionally-deficient *streptococci*, HACEK, *Bartonella*, *Coxiella*, *Chlamydia*, *Legionella*, *Brucella*
- Candida*

3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = *Pseudomonas*, saliva = oral flora, toilet water = GI flora)

### Clinical Features

- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia
- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute MR, AR)
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), headache (mycotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
  - Osler's nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth's spots (retinal hemorrhage with pale centre)

### Diagnosis

- Modified Duke Criteria, see Table 17
  - definitive diagnosis if: 2 major, or 1 major + 3 minor, or 5 minor
  - possible diagnosis if: 1 major + 1 minor, or 3 minor



### Clinical Features of Infective Endocarditis

#### FROM JANE

Fever  
Roth's spots  
Osler's nodes  
Murmur  
Janeway lesions  
Anemia  
Nail-bed hemorrhages (aka splinter hemorrhages)  
Emboli

**Table 17. Modified Duke Criteria**

Major Criteria(2)
<ol style="list-style-type: none"> <li>Positive blood cultures for IE <ul style="list-style-type: none"> <li>Typical microorganisms for IE from 2 separate blood cultures (<i>Streptococcus viridans</i>, HACEK group (see ID17), <i>Streptococcus bovis</i>, <i>Staphylococcus aureus</i>, community-acquired <i>enterococci</i>) OR</li> <li>Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn &gt;12 h apart or all of 3 or a majority of 4 or more separate blood cultures, with first and last drawn &gt;1 h apart OR</li> <li>Single positive blood culture for <i>Coxiella burnetii</i> or antiphase I IgG antibody titer &gt;1:800</li> </ul> </li> <li>Evidence of endocardial involvement <ul style="list-style-type: none"> <li>Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve)</li> <li>OR New valvular regurgitation (insufficient if increase or change in preexisting murmur)</li> </ul> </li> </ol>
Minor Criteria (5)
<ol style="list-style-type: none"> <li>Predisposing condition (abnormal heart valve, IVDU)</li> <li>Fever (38.0°C/100.4°F)</li> <li>Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions</li> <li>Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler's nodes, Roth's spots</li> <li>Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE</li> </ol>

**Investigations**

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of endovascular infection (such as IE)
- repeat blood cultures (at least 2 sets) after 48 to 72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), ESR (increased), RF (+), BUN/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- ECHO findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)



TEE  
TTE

transesophageal echo  
transthoracic echo

**Treatment**

- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment
  - empiric antibiotic therapy if patient is unstable
    - first-line: vancomycin + gentamicin or ceftriaxone
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism and sensitivities
  - monitor for complications of IE (e.g. CHF, conduction block, new emboli) and complications for antibiotics (e.g. interstitial nephritis)
  - prophylaxis only for high risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure or musculoskeletal tissue
    - dental/respiratory: amoxicillin single dose 30-60 min prior; clindamycin if penicillin-allergic
    - skin/soft tissue: cephalexin single dose 30-60 min prior ; clindamycin if penicillin-allergic (modify based on etiology of skin/soft tissue infection)
- surgical
  - most common indication is refractory CHF
  - other indications, include valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, Staphylococci on a prosthetic valve

**Prognosis**

- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess
- mortality: prosthetic valve IE (25-50%), non-IVDU *S. aureus* IE (30-45%), IVDU *S. aureus* or streptococcal IE (10-15%)



# Neurological Infections

## Meningitis

- see [Pediatrics](#), P62

### Definition

- inflammation of the meninges

### Etiology

**Table 18. Common Organisms in Meningitis**

Bacterial			Viral	Fungal	Other
Age 0-4 wk	Age 1-23 mo	Age >2 yr			
GBS <i>E. coli</i> <i>L. monocytogenes</i> <i>Klebsiella</i>	GBS <i>E. coli</i> <i>S. pneumoniae</i> <i>N. meningitidis</i> <i>H. influenzae</i>	<i>S. pneumoniae</i> <i>N. meningitidis</i> <i>L. monocytogenes</i> (age >50 and comorbidities)	HSV-1, 2 VZV Enteroviruses West Nile	<i>Cryptococcus</i> <i>Coccidioides</i>	Lyme disease Neurosyphilis TB

### Risk Factors

- lack of immunization against *S. pneumoniae*, *H. influenzae type b*
- hematogenous spread after invasion from a mucosal surface (nasopharynx)
- parameningeal focus (otitis media, infection, sinusitis)
- penetrating head trauma
- anatomical meningeal defects – CSF leaks
- previous neurosurgical procedures, shunts
- immunocompromise (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
- contact with colonized or infected persons

### Clinical Features

- neonates and children: fever, vomiting, lethargy, irritability, poor feeding
- older children and adults: fever, headache, neck stiffness, confusion, nausea and vomiting, lethargy, photophobia, altered level of consciousness, seizures, focal neurological signs, papilledema
- petechial rash on lower extremities with meningococcal meningitis

### Investigations

- bloodwork: CBC and differential, electrolytes (for SIADH), blood C&S
  - CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
  - AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
  - PCR for HSV, VZV, EBV, enteroviruses if viral cause suspected
- imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

**Table 19. CSF Profiles for Meningitis**

CSF Analysis	Bacterial	Viral
Glucose (mmol/L)	Decreased	Normal
Protein (g/L)	Markedly Increased	Increased
White blood cell	500-10,000/ $\mu$ L	10-500/ $\mu$ L
Predominant WBC	Neutrophils	Lymphocytes

### Treatment

- bacterial meningitis is a medical emergency: do not delay antibiotics before CT or LP
- empiric antibiotic therapy:
  - age <1 mo: ampicillin + cefotaxime  $\pm$  gentamicin IV
  - age >1 mo: vancomycin + ceftriaxone IV
    - ♦ add ampicillin IV (or TMP-SMX) if risk factors for infection with *L. monocytogenes* present: age >50, alcoholism, immunocompromised
- steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics (see sidebar)
  - benefit in all adults (including with pneumococcal meningitis) now uncertain



#### Brudzinski's Sign

Passive neck flexion causes involuntary flexion of hips and knees.

#### Kernig's Sign

Resistance to knee extension when hip is flexed to 90°.

#### Jolt Accentuation of H/A

Headache worsens when head turned horizontally at 2-3 rotations/s.



#### CSF Gram Stain Findings

- *S. pneumoniae* – GP diplococci
- *N. meningitidis* – GN diplococci
- *H. influenzae* – Pleiomorphic GN coccobacilli
- *L. monocytogenes* – GP rods



#### Adjunctive Dexamethasone in Bacterial Meningitis: a Meta-analysis of Individual Patient Data

*Lancet Neurol* 2010;9:254-63

**Study:** Meta-analysis of randomized, double blind, placebo controlled trial.

**Population:** 2029 patients from 5 trials, 833 <15 yr, HIV in 580, bacterial meningitis confirmed in 1639.

**Intervention:** Antibiotics with vs. without dexamethasone (first dose given within 20 min prior to or with first dose of antibiotics).

**Outcome:** Death, death or any neurological sequelae, and death or severe bilateral hearing loss at first follow-up; death or severe neurological sequelae at 1 mo.

**Results:** There was no difference in death [OR 0.97 (95% CI, 0.79–1.19)], death or severe bilateral hearing loss [OR 0.89, (95% 0.73–1.09)]. Death or severe neurological sequelae or any hearing loss [OR 0.92 (95% CI, 0.76–1.11)], or death or any neurological sequelae or any hearing loss [OR 0.89 (95% CI, 0.74–1.07)]. However, among survivors, dexamethasone may reduce hearing loss [OR 0.77 (95% CI, 0.60–0.99,  $p=0.04$ )].

**Conclusion:** The benefit of dexamethasone in acute bacterial meningitis is questionable with seemingly little effect in death or neurological sequelae. There may be some benefit on prevention of hearing loss.



#### Does this Adult Patient Have Acute Meningitis? From The Rational Clinical Examination

*JAMA* 2009; http://www.jamaevidence.com/content/3482857

**Study:** Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for the diagnosis of adult meningitis.

**Results:** In retrospective studies, sensitivity for headache was 68%, and 52% for nausea and vomiting. Sensitivity for physical exam findings is similarly low (fever: 87%, neck stiffness: 80%, altered mental status: 69%). Sensitivity for the combination of the classic triad of fever, neck stiffness and altered mental status was 46%. In prospective studies, sensitivity of headache was 92%, while sensitivity of nausea and vomiting could not be pooled, and ranged from 32–70%. Brudzinski's and Kernig's signs had a sensitivity of 5% and Kernig's sign only 5–9%. Jolt accentuation had a sensitivity of 97%.

**Conclusions:** Data were heterogeneous, and lacked standardization of clinical exams. No single item on clinical history or physical exam was sufficient to rule out meningitis, including Kernig's and Brudzinski's signs. The absence of the classic triad of fever, neck stiffness and altered mental status is not sufficient to rule out meningitis. Jolt accentuation has high sensitivity, but further research is needed. LP may be performed safely without CT head in patients without altered LOC, no recent seizure, no history of CNS disease, not immunocompromised, and <60 yr.

## Prevention

- see [Pediatrics](#), P3
- immunization
  - children: immunization against *H. influenzae* (Pentacel®), *S. pneumoniae* (Synflorix®, Prevnar-13®), *N. meningitidis* (Menjugate®, Menactra®)
  - adult: immunization against *N. meningitidis* in selected circumstances (outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with *H. influenzae* should be treated with rifampin if they live with an inadequately immunized or immunocompromised child <4 yr; ciprofloxacin, rifampin or ceftriaxone if close or household contact of a patient with *N. meningitidis*

## Prognosis

- complications
  - headache, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness, death
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation



### Public Health Agency of Canada Indications for Adult Immunization

#### Pneumococcal polysaccharide vaccine (i.e. Pneumovax®)

- >65 yr
- >2 yr, with chronic cardio/respiratory/hepatic/renal disorders, asplenia, sickle cell or immunosuppression

#### Meningococcal C-conjugate vaccine (i.e. Menjugate®)

- Young adults (not immunized in childhood)
- Asplenia\*
- Travellers to high-risk areas\*
- Military recruits\*
- Complement, factor D, or properdin deficiency\*

\*Quadrivalent vaccine (Menactra® or Menomune®) preferred

# Encephalitis

## Definition

- inflammation of brain parenchyma

## Etiology

- identified in only 40-70% of cases
  - when cause is identified, most common etiology is viral
  - e.g. HSV, VZV, EBV, enteroviruses, CMV, West Nile, HIV, mumps, measles, rabies, polio
  - bacteria: *L. monocytogenes*, *Mycobacteria*, spirochetes (Lyme, syphilis)
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. ADEM)

## Pathophysiology

- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response
- viruses may reach CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
  - associated with HSV-1, but can also be caused by HSV-2

## Clinical Features

- constitutional: fever, chills, malaise, nausea, vomiting
- meningeal involvement (meningoencephalitis): headache, nuchal rigidity
- parenchymal involvement: seizures, altered mental status, focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioural disturbance
  - usually rapidly progressive over several days and may result in coma or death
  - common sequelae: memory and behaviour disturbances

## Investigations

- CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses, and other less common viral etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. West Nile virus)
- imaging/neurologic studies: CT, MRI, EEG to define anatomical sites affected
- invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges

## Treatment

- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out



Meningitis and encephalitis patients can be distinguished based on their cerebral function. Cerebral function is abnormal in encephalitis patients (e.g. altered mental status, motor or sensory deficits, altered behavior, speech or movement disorders), but relatively normal in patients with meningitis. Note however, that there is considerable overlap between the two syndromes ("meningoencephalitis").

## Generalized Tetanus

- see [Family Medicine](#), FM3
- see [Pediatrics](#), P3



### Etiology and Pathophysiology

- caused by *Clostridium tetani*: motile, spore forming, anaerobic GP bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wound, burns, nonsterile surgeries or deliveries)
- upon inoculation, spores transform into *C. tetani* bacilli that produce tetanus toxin
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

### Clinical Features

- generalized tetanus
  - initially present with painful spasms of masseters (trismus or "lockjaw")
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
- autonomic hyperactivity
  - diaphoresis, tachycardia, hypertension, fever as illness progresses

### Investigations

- culture wounds, CK may be elevated, BUN usually normal

### Treatment

- stop toxin production
  - wound debridement to clear necrotic tissue and spores
  - antimicrobial therapy: IV metronidazole
- neutralize unbound toxin with TIG
- supportive therapy: intubation, spasmolytic medications (benzodiazepines), quiet environment, cooling blanket
- control autonomic dysfunction:  $\alpha$ - and  $\beta$ -blockade (e.g. labetalol), magnesium sulfate



Antimicrobial therapy (e.g. metronidazole) may fail to treat *C. tetani* unless adequate wound debridement is performed.

### Prevention

- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see [Pediatrics](#), P3/[Emergency Medicine](#), ER17)



## Rabies

### Definition

- acute progressive encephalitis caused by RNA virus (family: *Rhabdoviridae*, genus *Lyssavirus*)

### Etiology and Pathophysiology

- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoon, skunk, bat, fox, cat, and dog; monkeys also a risk in the developing world
- transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
  - almost all cases due to bites
- virus travels via retrograde axonal transport from PNS to CNS
- virus multiplies rapidly in brain, then spreads to other organs, including salivary glands
- development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
  - infected animal can transmit rabies virus as soon as it shows signs of disease

### Clinical Features

- 5 stages of disease:
  1. incubation period
    - 1-3 mo on average (can range from days to years)
  2. prodrome (<1 wk)
    - influenza-like illness: low-grade fever, malaise, anorexia, N/V, headache, sore throat
    - pain, pruritus, paresthesia may occur at wound site
    - once prodromal symptoms develop, there is rapid, irreversible progression to death
      - ♦ progression from prodrome to coma and death may occur without an intervening acute neurologic syndrome

3. acute neurologic syndrome: 3 types (<1 wk)
  - A. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia, hypersalivation, fever, seizures
    - ♦ painful pharyngeal spasms on encountering gust of air or swallowing water cause aerophobia and hydrophobia, respectively
  - B. paralytic: quadriplegia, loss of anal sphincter tone, fever
  - C. atypical: rare
4. coma
  - complete flaccid paralysis, respiratory and cardiovascular failure
5. death (within days to weeks of initial symptoms)

### Investigations

- purpose of diagnosis by investigations is to limit patient contact with others and to identify others exposed to the infectious source
- ante-mortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, serum, CSF
- post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in neurons)

### Treatment

- post-exposure prophylaxis depends on regional prevalence (contact Public Health) and circumstances surrounding injury
- 3 general principles:
  - wound care: clean wound promptly and thoroughly with soap and running water
  - passive immunization: HRIG infiltrated into wound site, with any remaining volume administered IM in anatomical site distant from vaccine administration
  - active immunization: inactivated rabies virus vaccine (series of shots post-exposure)
- treatment is supportive once victim manifests signs and symptoms of disease

### Prevention

- pre-exposure vaccination
  - recommended for high risk persons: laboratory staff working with rabies, veterinarians, animal and wildlife control workers, long-term travellers to endemic areas

## Systemic Infections

### Sepsis and Septic Shock

- see [Respirology](#), R33

### Definitions

- systemic inflammatory response syndrome (SIRS): 2 or more of
  - (a) temperature  $<35^{\circ}\text{C}/95^{\circ}\text{F}$  or  $>38.5^{\circ}\text{C}/101.3^{\circ}\text{F}$
  - (b) heart rate  $>90$  beats per minute
  - (c) respiratory rate  $>20$  breaths per minute or  $\text{PaCO}_2 <32$  mmHg
  - (d) WBC  $<4 \times 10^9/\text{L}$  or  $>12 \times 10^9/\text{L}$  or  $>10\%$  bands
- sepsis: SIRS + proven or provable infection
- severe sepsis: sepsis + signs of end-organ dysfunction and hypoperfusion
- septic shock: severe sepsis + hypotension ( $<90$  mmHg sBP), despite adequate fluid resuscitation

### Pathophysiology

- causative agents are identified in only 50-70% of cases
- when organisms are identified, GP and GN organisms are the cause in 90% of cases (GP > GN > fungal)
- primary bloodstream infection or secondary bacteremia  $\rightarrow$  local immune response  $\rightarrow$  immune cells release pro-inflammatory cytokines that defend against pathogens  $\rightarrow$  immune response spreads beyond local environment  $\rightarrow$  unregulated, exaggerated systemic immune response  $\rightarrow$  vasodilation and hypotension  $\rightarrow$  involvement of tissues remote from the site of injury/infection resulting in multiple major organ dysfunction  $\rightarrow$  followed by a period immunoparalysis

### Clinical Features

- history: fever, chills, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: abnormal vitals (fever, tachypnea, tachycardia, hypotension), local signs of infection

### Investigations

- CBC and differential, electrolytes, BUN, creatinine, liver enzymes, ABG, lactate, INR, PTT, FDP, blood C&S x3, urinalysis, urine C&S and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus of infection)



#### Types of SHOCK

Sepsis/Spinal cord trauma  
Hemorrhage  
Obstructive  
Cardiogenic  
Anaphylaxis

**Treatment** (also see [Respirology](#), R33)

- respiratory support: O<sub>2</sub> ± intubation
- cardiovascular support: IV fluids, ± norepinephrine + ICU
- IV antibiotics (empirical, depends on suspected source)
  - start with broad spectrum antibiotics (piperacillin-tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology of infection, and local microbial susceptibilities (± aminoglycoside or vancomycin)
  - if *Pseudomonas* unlikely: (ceftriaxone or piperacillin-tazobactam or meropenem) ± vancomycin
  - if drug-resistant GN (e.g. *Pseudomonas*) possible: ceftazidime or meropenem or piperacillin-tazobactam + gentamicin
  - narrow once susceptibilities are known
- hydrocortisone IV in patients with septic shock unresponsive to fluid resuscitation and vasopressors



## Tuberculosis (TB)

**Etiology, Epidemiology and Natural History**

- 1/3 of the world's population is infected with TB
- contracted by aerosolized inhalation of *Mycobacterium tuberculosis*, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive and replicate in macrophages
- inhalation and deposition in the lung can lead one of the following outcomes:
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 95% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 2-3 yr of initial infection) at a pulmonary or extra-pulmonary site

**Tuberculous Polyserositis**

= pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)

**Risk Factors**

- social and environmental factors
  - travel or birth in country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  - aboriginal, crowded living conditions, low SES/homeless
  - personal or occupational contact
- host factors
  - immunocompromised/immunosuppressed (including extremes of age)
  - silicosis
  - chronic renal failure requiring dialysis
  - malignancy and chemotherapy
  - substance abuse (e.g. drug use, alcoholism, smoking)

**Clinical Features**

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms
  - i. pulmonary TB
    - chronic productive cough ± hemoptysis
    - CXR consolidation or cavitation, lymphadenopathy
    - non-resolving pneumonia despite standard antimicrobial therapy
  - ii. miliary TB
    - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
    - CXR: multiple small 2-4 mm millet seed-like lesions throughout lung
  - iii. extrapulmonary TB
    - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott's disease), adrenal (causing Addison's disease), renal, ovary

**Investigations**

- screening for latent TB
  - PPD/Mantoux skin tests
    - ♦ both tests diagnose prior TB exposure; neither can diagnose or exclude active disease
  - IFN-γ release assay (IGRA):
    - ♦ in patients previously infected with TB, T-cells produce increased amounts of IFN-γ when re-exposed to TB antigen
    - ♦ detects antigen not present in the BCG vaccine or in most types of non-tuberculous-mycobacteria (NTM), therefore fewer false positives

**Positive PPD Test**

If induration at 48-72 h

> 5 mm if immunocompromised, close contact with active TB

> 10 mm all others; decision to treat depends on individual risk factors

**False(-):** poor technique, anergy, immunosuppression, infection <10 wk or remotely

**False(+):** BCG after 12 mo of age in a low-risk individual, NTM

**Booster effect:** initially false(-) result boost to a true(+) result by the testing procedure itself (usually if patient was infected long ago so had diminished delayed type hypersensitivity reaction or if history of BCG)



- Canadian TB guidelines recommend IGRA as a confirmatory test if false positive or false negative test results are suspected, while American guidelines treat IGRAs as equivalent to the TB skin test and preferable in patients with a history of BCG vaccination or who may not return for skin test reading
- diagnostic tests/investigations for active pulmonary TB:
  - morning sputum on 3 consecutive days for acid-fast bacilli smear and culture
  - BAL
  - CXR:
    - ♦ nodular or alveolar infiltrates with cavitation (middle/lower lobe if primary, apical if secondary)
    - ♦ pleural effusion (usually unilateral and exudative) may occur independently of other radiograph abnormalities
    - ♦ hilar/mediastinal adenopathy (especially in children)
    - ♦ tuberculoma (semi-calcified well-defined solitary coin lesion 0.5-4 cm that may be mistaken for lung CA)
    - ♦ miliary TB
    - ♦ evidence of past disease: calcified hilar and mediastinal nodes, calcified pulmonary focus, pleural thickening with calcification, apical scarring

### Prevention

- primary prevention
  - airborne isolation for active pulmonary disease
  - BCG vaccine
    - ♦ ~80% effective against pediatric miliary and meningeal TB
    - ♦ effectiveness in adults debated (anywhere from 0-80%)
    - ♦ routine use rarely recommended in Canadian population, however widely used in other countries
- secondary prevention (defer in pregnancy unless mother is high risk)
  - likely INH-sensitive: isoniazid (INH) + pyridoxine (vit B<sub>6</sub> to help prevent INH-associated neuropathy) x 9 mo
  - likely INH-resistant: rifampin x 4 mo

### Treatment of Active Infection

- empiric therapy: INH + rifampin + pyrazinamide + ethambutol + pyridoxine
- pulmonary TB: INH + rifampin + pyrazinamide + ethambutol + pyridoxine x 2 mo (initiation phase), then INH + rifampin + pyridoxine x 4 mo in fully susceptible TB (continuation phase), total 6 mo
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
  - MDR = resistance to INH and rifampin ± others
  - XDR = resistance to INH + rifampin + fluoroquinolone + ≥1 of injectable, second-line agents
  - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Public Health Agency of Canada website for more information: [www.publichealth.gc.ca](http://www.publichealth.gc.ca))



#### Anti-tuberculosis Drugs for Active Infection

##### RIPE for treatment

Rifampin  
Isoniazid (INH)  
Pyrazinamide  
Ethambutol

## Leprosy (Hansen's Disease)

### Etiology

- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

### Clinical Features

- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  - paucibacillary "tuberculoid" leprosy (intact cell-mediated immune response)
    - ≤5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
    - early nerve involvement, enlarged peripheral nerves, neuropathic pain
    - may be self-limited, stable, or progress over time to multibacillary "lepromatous" form
  - multibacillary "lepromatous" leprosy (weak cell-mediated immune response)
    - ≥6 lesions, symmetrical distribution
    - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
    - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  - borderline leprosy
    - lesions and progression lies between tuberculoid and lepromatous forms



## Investigations

- skin biopsy down to fat or slit skin smears for AFB, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

## Treatment (WHO Treatment Regimens)

- paucibacillary: dapsone + rifampin monthly x 6 mo
- single skin lesion paucibacillary: single dose of rifampicin, ofloxacin, and minocycline
- multibacillary and borderline: dapsone + rifampin monthly + clofazimine monthly x 12 mo AND low dose clofazimine once daily x 12 mo
- treatment of leprosy can cause an immune reaction to killed bacteria (e.g. erythema nodosum leprosum and reversal reaction): symptomatic management with NSAIDs if mild, prednisone with 6-12 wk taper if severe; thalidomide for erythema nodosum leprosum

## Prognosis

- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum leprosum
- long post-treatment follow-up warranted to monitor for relapse and immune reactions

# Syphilis

## Etiology

- *Treponema pallidum*: thick motile spirochetes historically detectable by dark-field microscopy (rarely done now)
- transmitted sexually, vertically, or parenterally (rare)

## Clinical Features

- see [Dermatology](#), D31 and [Gynecology](#), GY28
- multi-stage disease
  - primary syphilis (3-90 d post-infection)
    - painless chancre at inoculation site (any mucosal surface)
    - regional lymphadenopathy
    - acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment
  - secondary syphilis = systemic infection (2-8 wk following chancre)
    - maculo-papular non-pruritic rash including palms and soles
    - generalized lymphadenopathy, low grade fever, malaise, headaches, aseptic meningitis, ocular/otic syphilis
    - condylomata lata: painless, wart-like lesion on palate, vulva or scrotum (highly infectious)
  - latent syphilis
    - asymptomatic infection that follows untreated primary/secondary syphilis
    - early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
    - increased transmission risk with early latent; longer treatment duration required for late latent
  - tertiary syphilis (1-30 yr post-infection)
    - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
    - aortic aneurysm and aortic insufficiency
    - neurosyphilis: dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis
  - congenital syphilis
    - causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
    - infants may be asymptomatic until age 2-5 yr then present with rhinitis, lymphadenopathy, hepatosplenomegaly, bone and cartilage degeneration (including saddle nose, saber shins), CN VIII deafness

## Investigations

- screening tests: VDRL and RPR (non-treponemal), EIA (treponemal)
- confirmatory tests: FTA-ABS, MHA-TP, TPPA, TPI, dark field microscopy with silver stain
- LP for 3° syphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms/RPR ≥1:32, or with HIV disease and late latent/unknown duration syphilis

## Treatment

- for 1°, 2°, early latent: benzathine penicillin G 2.4 million units IM x 1
- for 3°, late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- if allergic to penicillin: doxycycline 100 mg PO bid x 14 d
- neurosyphilis: aqueous Penicillin G 18-24 million units/d IV x 14 d

## Generalized STI Workup

- see [Family Medicine](#), FM46



**Argyll Robertson Pupil**  
Accommodates but does not react to light.



**Those with Untreated 1° or 2° Syphilis**  
1/3 cure  
1/3 latent indefinitely  
1/3 3° syphilis



**Causes of False Positive VDRL and RPR Tests:**

Viruses (mononucleosis, hepatitis)  
Drugs and substance abuse  
Rheumatic fever  
Lupus and leprosy



Patients with 2° or 3° syphilis treated with penicillin may experience a Jarisch-Herxheimer reaction. Lysis of organisms release pyrogens thought to cause fever, chills, myalgia, flu-like symptoms may last up to 24 h.



**VDRL** Venereal Disease Research Laboratory  
**RPR** Rapid Plasma Reagin  
**EIA** Enzyme Immunoassay  
**TPI** *T. pallidum* Immobilization Assay  
**FTA-ABS** Fluorescent *Treponema* Antibody-Absorption  
**MHA-TP** Microhemagglutination Assay *T. pallidum*  
**TPPA** *T. pallidum* Particle Agglutination Assay



## Lyme Disease



### Etiology/Epidemiology

- spirochete bacteria: *Borrelia burgdorferi* (N. America), *B. garinii*, *B. afzelii* (Europe and Asia)
- transmitted by Ixodes tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- in Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick and Nova Scotia as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment

### Clinical Features

- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, headache, myalgias
  - erythema migrans (EM): expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) on thigh/groin/axilla
- stage 2 (early disseminated stage): weeks post-infection
  - CNS: aseptic meningitis, CN palsies (CNVII palsy), peripheral neuritis
  - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronica atrophicans (due to *B. afzelii*)
  - neurologic: encephalopathy, meningitis, neuropathy



#### BAKE a Key Lyme Pie

Bell's palsy  
Arthritis  
Kardiac block  
Lyme  
Erythema chronicum migrans

### Investigations

- serology: ELISA, Western Blot

### Prevention

- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks and prompt removal of tick
- prophylaxis within 72 h of finding engorged attached nymphal tick that has been attached  $\geq 36$  h (approximately) in hyperendemic area (local rate of infection of ticks  $\geq 20\%$ ): doxycycline

### Treatment

- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone

## Toxic Shock Syndrome (TSS)

### Etiology

- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF). Course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- Staphylococcal TSS involves the production of superantigen TSST-1 (toxic shock syndrome toxin 1)
- Streptococcal TSS involves the production of superantigens SPEA, SPEB, SPEC

### Risk Factors

- Staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or caesarean or other surgical infections)
- Streptococcal: minor trauma, surgical procedures, preceding viral illness (chickenpox), use of NSAIDs

### Clinical Features and Investigations

- acute onset, fever, sBP <90 mmHg
- Staphylococcal TSS:
  - rash with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
- Streptococcal TSS:
  - erythematous macular rash
  - isolation of GAS (e.g. blood, pleural, tissue biopsy, or surgical wound)
  - $\geq 2$  of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment

**Treatment**

- supportive: fluid resuscitation
- Staphylococcal: for methicillin-susceptible *S. aureus*: clindamycin + cloxacillin (IV); for MRSA: vancomycin x 10-14 d
- Streptococcal: IV penicillin and clindamycin and IVIg

## Cat Scratch Disease

**Etiology**

- *Bartonella henselae*: intracellular bacteria
- cat-to-human transmission via cat scratch/bite

**Clinical Features**

- skin lesion appears 3-10 d post-inoculation
- may be followed by fever, tender regional lymphadenopathy
- in some patients, organism may disseminate causing hepatosplenomegaly, neurologic symptoms
- usually self-limited

**Investigations**

- serology, lymph node biopsy

**Treatment**

- supportive in most cases
- azithromycin x 10-14 d in patients with moderate-severe disease or immunocompromise

## Rocky Mountain Spotted Fever

**Etiology**

- *Rickettsia rickettsii*: obligate intracellular GN organism
- reservoir hosts: rodents, dogs
- vectors: *Dermacentor* ticks
- organisms cause inflammation of endothelial lining of small blood vessels, causing small hemorrhages and thrombi
- can cause widespread vasculitis leading to headache, CNS changes and can progress to death if treatment is delayed

**Clinical Features**

- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, headache, myalgia, nausea/vomiting, anorexia
- macular rash appearing on day 2-4 of fever
  - begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  - occasionally "spotless" (10% of patients)

**Investigations**

- skin biopsy and serology (indirect fluorescent antibody test)

**Treatment**

- doxycycline, usually 5-7 d course

## West Nile Virus

**Epidemiology**

- virus has been detected throughout the United States and much of southern Canada
- overall case-fatality rates in severe cases are ~10%

**Transmission**

- primarily from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation

**Clinical Features**

- most are asymptomatic
- most symptomatic cases are mild (West Nile fever): acute onset of headache, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis and acute flaccid paralysis (especially in those >60 yr)

**Investigations**

- IgM antibody in serum or CSF (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue Fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- viral isolation by PCR from CSF, tissue, blood and fluids (all have low sensitivity)
- CSF: elevated lymphocytes and protein if CNS involvement

**Treatment and Prevention**

- treatment: supportive
- prevention: mosquito repellent (DEET), drain stagnant water, community mosquito control programs

## Fungal Infections

### Skin and Subcutaneous Infections

#### Superficial Fungal Infections

- see [Dermatology](#), D25



#### Dermatophytes

- see [Dermatology](#), D26



#### Subcutaneous Fungal Infection

**Pathophysiology**

- fungi that naturally reside in soil and enter skin via traumatic break
- *Sporothrix schenckii*: most commonly affects gardeners injured by a rose thorn or splinter
  - causes subcutaneous nodule at point of entry
  - fungi may migrate up lymphatic vessels creating nodules along the way – “nodular lymphangitis”

**Treatment**

- oral azole (e.g. itraconazole)
- IV amphotericin B for severe or disseminated infection

## Endemic Mycoses

**Basics**

- three major endemic mycoses in North America
  - histoplasmosis
  - blastomycosis
  - coccidioidomycosis
- thermally dimorphic organisms: mold in cold temperature (e.g. soil) and yeast at higher temperature (e.g. tissue)
- infection occurs through inhalation of spores (soil, bird droppings, vegetation) or inoculation injury
- all can cause pneumonia and may disseminate hematogenously
- may reactivate or disseminate during immunocompromise

**Treatment**

- common to all systemic mycoses
  - oral azole (e.g. itraconazole for mild-moderate local infection)
  - IV amphotericin B for systemic infection



Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts and bat caves.

**High Risk for Dissemination**

- Immunocompromised (e.g. AIDS, steroids, TNF- $\alpha$  inhibitors)
- Pregnancy (3rd trimester)
- Diabetes

Table 20. Endemic Mycoses

Disease	Endemic Region	Clinical Features	Investigations
<i>Histoplasma capsulatum</i>	Ohio and Mississippi river valleys in central USA, Ontario, Quebec; widespread	Asymptomatic (in most people) Primary pulmonary <ul style="list-style-type: none"> <li>Fever, cough, chest pain, headache, myalgia, anorexia</li> <li>CXR (acute): pulmonary infiltrates <math>\pm</math> hilar lymphadenopathy</li> <li>CXR (chronic): pulmonary infiltrates, cavitary disease</li> </ul> Disseminated (rare) <ul style="list-style-type: none"> <li>Occurs primarily in immunocompromised patients</li> <li>Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS</li> </ul>	Fungal culture, fungal stain Antigen detection (urine and serum)
<i>Blastomyces dermatitidis</i>	States east of Mississippi River, Northern Ontario and along the great lakes	May be asymptomatic Primary: acute or chronic pneumonia <ul style="list-style-type: none"> <li>Fever, cough, chest pain, chills, night sweats, weight loss</li> <li>CXR (acute): lobar or segmental pneumonia</li> <li>CXR (chronic): lobar infiltrates, fibronodular interstitial disease</li> </ul> Disseminated <ul style="list-style-type: none"> <li>Spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), GU tract (prostatitis, epididymitis)</li> </ul>	Sputum smear and culture Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material)
<i>Coccidioides immitis</i>	Deserts in southwest USA, northwest Mexico	Primary <ul style="list-style-type: none"> <li>"Valley fever": subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for weeks to months</li> <li>Can develop hypersensitivity with arthralgias, erythema nodosum</li> </ul> Disseminated <ul style="list-style-type: none"> <li>Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningitis)</li> <li>Common opportunistic infection in patients with HIV</li> </ul>	Sputum culture Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material)

## Opportunistic Fungi

### *Pneumocystis jiroveci* (formerly *P. carinii*)

#### Microbiology

- unicellular fungi
- previously classified as a protozoa

#### Transmission

- rarely person-to-person transmission
- most disease is due to reactivation of latent infection acquired by the respiratory route or reinfection by a different genotype
  - causes clinical disease in immunocompromised patients (steroid use, HIV)
  - 80% lifetime risk without prophylaxis in patients with CD4 count  $<200$  cells/mm<sup>3</sup>

#### Clinical Features

- symptoms of pneumonia: fever, nonproductive cough, progressive dyspnea
- classic CXR (see sidebar)

#### Investigations

- demonstration of organism in induced sputum, bronchoalveolar lavage, or endotracheal aspirate (if intubated)

#### Treatment and Prevention

- oxygen to keep SaO<sub>2</sub>  $>90\%$
- antimicrobial options:
  - TMP/SMX (PO or IV) \*First line
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV)
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia (pO<sub>2</sub>  $<70$  mmHg or A-a gradient O<sub>2</sub>  $>35$  mmHg)
- prophylactic TMP/SMX for those at high risk of infection (HIV patients when CD4  $<200$  cells/mm<sup>3</sup> or non-HIV immunocompromised patients under specific conditions)



#### CXR in *P. jiroveci*

- Bilateral, diffuse opacities
- CXR may be normal (20-30% cases)
- CT shows cysts (hence the name "Pneumo" "cystis") but almost never pleural effusions

## ***Cryptococcus* spp.**

### **Microbiology**

- encapsulated yeast found worldwide
- 2 human pathogenic species: *C. gattii*, *C. neoformans*

### **Transmission**

- inhalation of airborne yeast from soil contaminated with pigeon droppings (*C. neoformans*) or certain tree species such as Eucalyptus or Douglas fir (*C. gattii*) → may cause local infection in lung → asymptomatic or pneumonia
- may also spread hematogenously to the CNS, skin, bones and other organs
- *C. neoformans* tends to affect immunocompromised hosts
- *C. gattii* tends to affect immunocompetent hosts

### **Clinical Features**

- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of *Molluscum contagiosum*

### **Investigations**

- serum cryptococcal antigen
- CSF for meningitis: India-ink stain, cryptococcal antigen test, culture to confirm
- blood C&S

### **Treatment**

- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance



*C. gattii* sees limited geographical distribution including Vancouver Island, Northern Australia, and Papua New Guinea.



India-ink sensitivity for cryptococcus is only 50% (higher in HIV patients).

## ***Candida albicans***



### **Microbiology**

- yeast forms with pseudohyphae at 20°C and germ tube formation at 37°C

### **Transmission**

- normal flora of skin, mouth, vagina and GI tract
- risk factors for overgrowth:
  - immunocompromised state (diabetes, corticosteroids)
  - ICU patients (broad-spectrum antibiotic use, central venous catheters, TPN)

### **Clinical Features**

- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see [Gynecology](#), GY24), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash distinguish it from tinea or other conditions
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease



### **Treatment**

- thrush: nystatin suspension or pastilles for mild disease, fluconazole for severe disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

## ***Aspergillus* spp.**

### **Microbiology**

- branching septate hyphae
- common species causing disease include *A. fumigatus*, *A. flavus*



### Transmission

- ubiquitous in the air and the environment
- *Aspergillus* produces a toxin called aflatoxin that contaminates nuts, grains and rice

### Clinical Features

- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a preexisting lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, pleuritic pain, tends to cavitate; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules
- mycotoxicosis
  - aflatoxin produced by *A. flavus* (nuts, grains, rice)
  - results in liver hemorrhage, necrosis and hepatocellular carcinoma formation

### Treatment Options

- for invasive aspergillosis: voriconazole or amphotericin B
- surgical resection for aspergilloma and hemorrhage
- corticosteroids for ABPA

## Parasitic Infections

### Protozoa – Intestinal/Genitourinal Infections

#### *Entamoeba histolytica* (Amoebas)

### Transmission

- reservoir: infected humans
- cysts by fecal-oral and food/waterborne transmission in areas of poor sanitation
- seen in immigrants, travellers, institutionalized individuals, Aboriginal Canadians, MSM

### Clinical Features

- asymptomatic carriers
- amoebic dysentery
  - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea secondary to local tissue destruction and ulceration of large intestine
- amoebic abscesses
  - most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
  - can also occur in lungs and brain

### Investigations

- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- *E. histolytica* indistinguishable microscopically from the non-pathogen *E. dispar* (distinguish by specific stool antigen detection)

### Treatment and Prevention

- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)

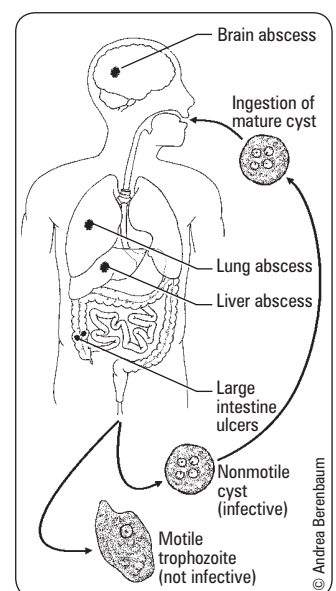


Figure 8. *Entamoeba* life cycle

## ***Giardia lamblia***

### **Transmission**

- reservoir: infected humans and other mammals
- food/waterborne (especially in the Rockies) and fecal-oral transmission of infectious cysts
- risk factors: travel, camping, institutions, day care centres, MSM

### **Clinical Features**

- giardiasis (“beaver fever”)
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucus in stool

### **Investigations**

- multiple stool samples (daily x 3 d) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

### **Treatment and Prevention**

- metronidazole, nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

## ***Trichomonas vaginalis***

### **Transmission**

- sexual contact

### **Clinical Features**

- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- trichomonas vaginitis (see [Gynecology](#), GY25)
  - vaginal discharge (profuse, malodorous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

### **Investigations**

- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

### **Treatment**

- metronidazole for patient and partner(s)



Trichomonas causes 25% of vaginitis.

## ***Cryptosporidium* spp.**

### **Transmission**

- reservoir: infected humans and a wide variety of young animals
- fecal-oral transmission by ingestion of cysts, waterborne
- risk factors: summer and fall, young children (day care), MSM, contact with farm animals, immunocompromise, immune reconstitution

### **Clinical Features**

- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with nausea, vomiting, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)

### **Investigations**

- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody

### **Treatment and Prevention**

- supportive care only for immunocompetent hosts
- in HIV, try HAART to restore immunity; if fails, try nitazoxanide
- good personal hygiene, water filtration

## Blood and Tissue Infections

### *Plasmodium* spp. (Malaria)

#### Microbiology

- species include: *P. falciparum* (most common and most lethal), *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* (new species isolated from primates in Malaysia, potentially fatal)
- complex life cycle: human host for asexual reproduction and mosquito for sexual reproduction
- sporozoite from mosquitos infect liver cells in which parasites multiply and are released as merozoites which infect RBCs causing disease
- P. ovale* and *P. vivax* can produce dormant hypnozoites in the liver that may cause relapsing malarial attacks by reactivating (entering the erythrocytic cycle) after many months

#### Transmission

- reservoir: infected human
- transmission by the night-biting female *Anopheles* mosquito, vertical transmission and blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

#### Clinical Features

- flu-like prodrome
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of RBCs) (lasts several hours)
  - P. vivax* and *P. ovale*: chills and fever q48h but can be variable
  - P. malariae*: chills and fever q72h but can be variable
  - P. falciparum*: less predictable fever interval, can be highly variable (>90% ill within 30 d)
- abdominal pain, diarrhea, myalgia, headache, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis

#### Complications

- P. falciparum*: CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute renal failure, ARDS, primarily responsible for fatal disease
- P. knowlesi*, and rarely *P. vivax* can be fatal

#### Investigations

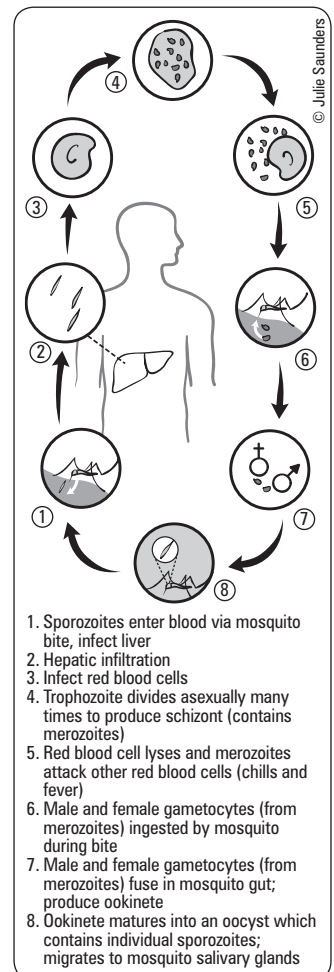
- microscopy: blood smear q12-24h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests

#### Treatment and Prevention

- P. vivax*, *P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- P. vivax*, chloroquine resistant: primaquine with quinine and doxycycline or tetracycline or mefloquine
- P. malariae*, *P. knowlesi*: chloroquine
- P. falciparum*: most areas of the world show chloroquine resistance
  - artemisinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - atovaquone/proguanil combination (Malarone®)
  - quinine plus doxycycline, tetracycline or clindamycin
  - mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- prevented by antimalarial prophylaxis, bed nets, insect repellent



Malaria is the most common fatal infectious disease worldwide.



**Figure 9. Life cycle of *Plasmodium* spp.**



#### Drugs for Preventing Malaria in Travelers

Cochrane DB Syst Rev 2010;CD006491

Study: Cochrane Systematic Review. 8 RCTs.

**Population:** 4240 non-immune adults and children traveling to regions with *P. falciparum* resistance to chloroquine.

**Intervention:** Atovaquone-proguanil, doxycycline, mefloquine, chloroquine-proguanil, or primaquine used for malaria prophylaxis.

**Outcome:** Efficacy, safety, and tolerability.

**Results:** Atovaquone-proguanil and doxycycline had similar adverse events. Atovaquone-proguanil had fewer overall (RR 0.72), GI (RR 0.54), neuropsychiatric (RR 0.49) than mefloquine. Doxycycline also had fewer neuropsychiatric events than mefloquine (RR 0.84).

**Conclusion:** Atovaquone-proguanil or doxycycline as prophylaxis against malaria is best tolerated in terms of adverse effects and mefloquine is associated with adverse neuropsychiatric outcomes.

### *Trypanosoma cruzi*

#### Transmission

- found in Mexico, South America and Central America
- transmission by *Reduviid* insect vector ("Kissing Bug"), which defecate on skin and tryptomastigotes in the stool usually rubbed into bite site by host (majority of infections)
- also transmitted via placental transfer, organ donation, blood transfusion and ingestion of contaminated food containing *Reduviid* insects (especially cane juice)

#### Clinical Features

- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation ("Romanas sign"; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly and hepatosplenomegaly
  - intermediate phase: asymptomatic but increasing levels of parasite and antibody in blood; most infected persons remain in this phase
  - chronic: can lead to chronic dilated cardiomyopathy, esophagomegaly and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

### Investigations

- wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

### Treatment and Prevention

- acute: nifurtimox or benznidazole
- intermediate: increasing trend to treat as acute infection
- chronic: symptomatic therapy, surgery including heart transplant, or esophagectomy, colectomy, as necessary, may be a benefit to antiparasitic treatment
- insect control, bed nets

## Toxoplasma gondii

### Transmission

- acquired through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), vertical transmission, organ transplantation, whole blood transfusions

### Clinical Features

- congenital
  - result of acute primary infection of mother during pregnancy (TORCH infection – see [Obstetrics](#), OB20)
  - stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult → blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
- acquired
  - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
  - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (headache and focal neurological signs)
  - lymph node, liver and spleen enlargement and pneumonitis
  - chorioretinitis

### Investigations

- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination
- negative serology in many AIDS patients (false negative due to decreased lymphocyte population)

### Treatment and Prevention

- no treatment if: immunocompetent, not pregnant, no severe organ damage
- pregnancy: spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folinic acid), avoid undercooked meat and refrain from emptying cat litter boxes
- HIV: pyrimethamine + sulfadiazine, AIDS prophylaxis: see HIV section
- eye disease, meningitis: corticosteroids
- proper hand hygiene, cook meat thoroughly



1/3 of Ontario's population is infected with *Toxoplasma gondii*.



#### Classic Triad of Congenital Toxoplasmosis:

- Chorioretinitis
- Hydrocephalus
- Intracranial calcifications

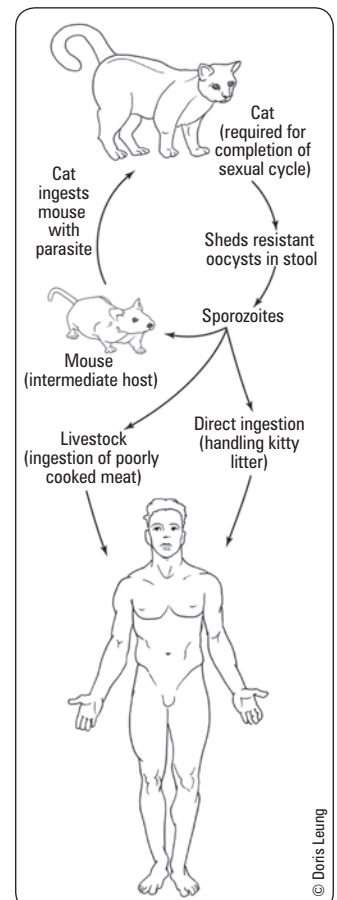


Figure 10. Life cycle of *Toxoplasma gondii*

## Helminths

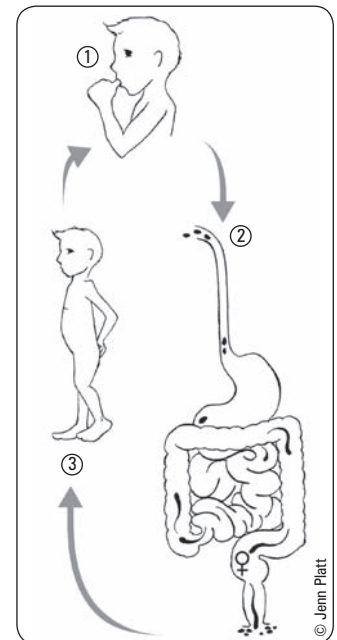
### Roundworms – Nematodes

Table 21. Nematodes (roundworms)

Nematode	Epidemiology	Transmission	Medical Importance	Treatment
<i>Ascaris lumbricoides</i>	Tropics	Human feces, ingestion of contaminated food or water	Abdominal pain and intestinal obstruction from high worm burden Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löfller's syndrome)	Mebendazole OR albendazole OR pyrantel pamoate
<i>Trichuris trichiura</i> (whipworm)	Tropics	Ingestion of eggs in soil	Diarrhea (± mucous, blood), abdominal pain, rectal prolapse, stunted growth	Mebendazole OR albendazole
<i>Onchocerca volvulus</i>	Africa, Latin America	Blackfly bite	River blindness (onchocerciasis), dermatitis	Ivermectin + doxycycline

**Table 21. Nematodes (roundworms) (continued)**

Nematode	Epidemiology	Transmission	Medical Importance	Treatment
<i>Wuchereria bancrofti</i>	Tropics	Mosquito bite	Damage to lymphatics resulting in lymphadenopathy, lymphedema, and elephantiasis Tropical pulmonary eosinophilia	Diethylcarbamazine + doxycycline
<i>Loa Loa</i>	Central Africa	Deer fly bite	Subcutaneous migration of worm, hyperresponsiveness in travelers	Diethylcarbamazine, removal of adult
<i>Enterobius vermicularis</i> (Pinworm)	Worldwide	Human host: fecal-oral self-inoculation and fomite person-to-person transfer Adult worms live in cecum and deposit eggs in perianal skin	Asymptomatic carriers or severe nocturnal perianal itching (pruritus ani) Occasional vaginitis Abdominal pain, nausea, vomiting with high worm burden	Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out) Examination of perianal skin at night may reveal adult worms Usually no eosinophilia as no tissue invasion Mebendazole, albendazole; pyrantel in pregnancy Change underwear, bathe in morning, pajamas to bed, wash hands, trim fingernails Treat all family members simultaneously Reinfection common
<i>Strongyloides stercoralis</i> (Threadworm)	Subtropical, tropical and temperate (including southern US)	Fecal contamination of soil: transmission via unbroken skin, walking barefoot Autoinfection: penetration of larvae through GI mucosa or perianal skin Adult worms live in mucosa of small intestine	One of few worms able to multiple in human host Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löffler's syndrome) Abdominal pain, diarrhea, pruritis ani, larva currens (itchy rash) Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; immunoblastic therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection	Ivermectin, 200 µg/kg/d PO x 2 doses (albendazole 40 mg PO bid x 7 d, less effective)

**Figure 11. Life cycle of *Enterobius***

## Flatworms

### Cestodes/Trematodes

**Table 22. Cestodes/Trematodes (flatworms)**

	Epidemiology	Transmission	Medical Importance	Treatment
<b>CESTODES</b>				
<i>Taenia solium</i>	Developing countries	Undercooked pork (larvae), human feces (eggs)	Taeniasis: mild abdominal symptoms Cysticercosis: mass lesions in CNS, eyes, skin, seizures	Corticosteroids + albendazole for cysticercosis Antiepileptics if seizures praziquantel for adult tapeworm in gut (taeniasis)
<i>Taenia saginata</i>	Developing countries	Undercooked beef (larvae)	Mild GI symptoms	Praziquantel
<i>Diphyllobothrium latum</i>	Europe, North America, Asia	Raw fish	B <sub>12</sub> deficiency leading to macrocytic anemia and posterior column deficits	Praziquantel
<i>Echinococcus granulosus</i>	Rural areas Sheep raising countries	Dog feces (eggs)	Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture) Risk of anaphylaxis if cystic fluid released during surgical evacuation	Albendazole alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole
<b>TREMATODES</b>				
<i>Clonorchis sinensis</i>	Japan, Taiwan, China, SE Asia	Raw fish	Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma	Praziquantel
<i>Schistosoma</i> spp.	Africa, SE Asia, focal in Western Hemisphere	Fresh water exposure	Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, SCC of the bladder)	Praziquantel

## Trematodes/Flukes

### *Schistosoma* spp.

#### Species

- *S. mansoni*, *S. hematobium*, *S. japonicum*

#### Transmission

- larvae (cercariae), released from snails, penetrate unbroken skin in infested fresh water (see Figure 13)
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach fresh water to hatch; schistosomes cannot multiply in or pass between humans

#### Clinical Features

- most asymptomatic; symptoms seen in travelers (nonimmune)
- Swimmer's itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, headache, weight loss, cough, abdominal pain, chronic diarrhea, eosinophilia

#### Complications of Chronic Infection

- caused by granulomatous response and fibrosis secondary to egg deposition by adults in the veins surrounding the intestine or bladder
- more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa
- *S. mansoni*, *S. japonicum*
  - worms in mesenteric vein, eggs in portal tracts of liver and bowel
  - heavy infections: intestinal polyps, portal and pulmonary hypertension, splenomegaly (2° to portal HTN), hepatomegaly
- *S. hematobium*
  - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
  - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
- neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
- pulmonary complications: granulomatous pulmonary endarteritis, pulmonary hypertension, cor pulmonale; especially in patients with hepatosplenic involvement

#### Investigations

- serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia)
- *S. mansoni*, *S. japonicum*: eggs in stool, liver U/S shows fibrosis, rectal biopsy
- *S. hematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

#### Treatment and Prevention

- praziquantel
- add glucocorticoid if acute schistosomiasis or neurologic complications develop
- proper disposal of human fecal waste, molluscicide, avoidance of infested water

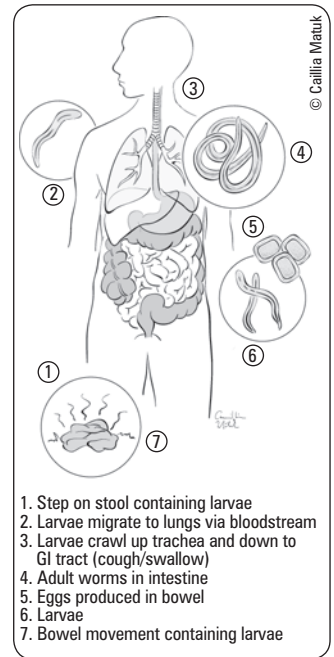


Figure 12. Life cycle of *Strongyloides*

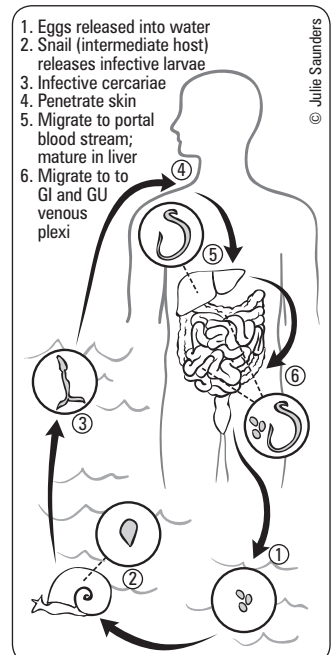


Figure 13. Life cycle of *Schistosoma*

## Ectoparasites

- scabies, lice
- see [Dermatology](#), D27



## Travel Medicine

#### General Travel Precautions

- vector-borne: long-sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings and bed nets, repellents applied to skin (DEET)
- food/water: avoid eating raw meats/seafood, uncooked vegetables and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions, fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller's diarrhea (bismuth salicylate)



- standard vaccines up to date (HepB, MMR, tetanus/diphtheria, varicella, pertussis, polio)
- travel vaccines: Hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

### Infectious Diseases to Consider

- vector borne: malaria, dengue fever, Chikungunya fever, yellow fever, *Rickettsia*, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, spotted fever, leishmaniasis
- sexually transmitted: HIV, HBV, syphilis, usual STIs
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis
- airborne: TB
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amoebiasis, dysentery, traveller's diarrhea, cholera, *Campylobacter* spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis



For up to date information on geographic and seasonal patterns of disease and travel advisories, check the website for the United States Centers for Disease Control and Prevention ([wwwnc.cdc.gov/travel](http://wwwnc.cdc.gov/travel)) or Foreign Affairs Canada ([travel.gc.ca](http://travel.gc.ca)).

## Fever in the Returned Traveller

### Etiology

- commonly identified causes of fever in returning traveller
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: typhoid from *Salmonella* (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller's diarrhea (10-20%), RTI (10-15%), UTI/STI (2-3%)
- febrile illness in travellers can be caused by routine infections that are common in nontravellers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes: e.g. DVT, PE

### History

- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
- persons visiting friends and family more likely to be exposed to local population and pathogens
  - style of travel: lodgings, camping, adventure travelling
  - local population: sick contacts
  - transportation: use of animals
- exposure history
  - street foods, untreated water: increased risk of traveller's diarrhea, enteric fever
  - uncooked meat/unpasteurized dairy: increased risk of parasitic infection
  - body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  - increased risk of HBV, HCV, HIV, GC, *C. trachomatis*, syphilis
  - animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies
- fever pattern
- incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  - <21 d: consider malaria, typhoid fever, dengue fever, rickettsioses; exclude HBV, TB
  - >21 d: consider malaria, TB; exclude dengue fever, travellers' diarrhea, rickettsioses
- body systems affected: GI, respiratory, CNS, skin

### Investigations

- all travellers with fever should undergo the following tests:
  - bloodwork: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  - urine: urinalysis, urine C&S
- special tests based on symptoms, exposure history, and geography
  - stool: C&S, O&P
  - CXR
  - dengue serology for IgM



Fever in traveller from malaria endemic area is malaria until proven otherwise.



#### Important Exposures

##### Insect Bites

Mosquito	<ul style="list-style-type: none"> <li>• <i>Plasmodium</i> spp. (Malaria)</li> <li>• Dengue</li> <li>• Lymphatic filariasis (Elephantiasis)</li> <li>• West Nile Encephalitis</li> <li>• Yellow Fever</li> <li>• Japanese Encephalitis</li> </ul>
Tick	<ul style="list-style-type: none"> <li>• <i>Borrelia burgdorferi</i> (Lyme Disease)</li> <li>• <i>Rickettsia rickettsii</i> (Rocky Mountain Spotted Fever)</li> </ul>
Fly	<ul style="list-style-type: none"> <li>• <i>Trypanosoma brucei</i> spp. (African sleeping sickness)</li> <li>• <i>Leishmania</i> spp. (Leishmaniasis)</li> <li>• <i>Bartonella bacilliformis</i> (Bartonellosis)</li> </ul>
Flea	<ul style="list-style-type: none"> <li>• <i>Yersinia</i> (Plague)</li> <li>• <i>Tunga penetrans</i> (Tungiasis)</li> </ul>

##### Mammal Bites

Dog/Cat	<ul style="list-style-type: none"> <li>• Rabies, Pasteurella, anaerobes, <i>Streptococcus</i>, <i>S. aureus</i></li> </ul>
Human	<ul style="list-style-type: none"> <li>• <i>Streptococcus</i>, <i>S. aureus</i>, oral anaerobes, <i>Eikenella</i></li> </ul>

##### Oral Exposures

Unpasteurized milk	<ul style="list-style-type: none"> <li>• <i>Brucella</i> spp., non-tuberculous mycobacteria, <i>Salmonella</i>, <i>E. coli</i>, <i>Listeria</i></li> </ul>
Undercooked meat/fish	<ul style="list-style-type: none"> <li>• Enteric bacteria, helminths, protozoa</li> </ul>
Water	<ul style="list-style-type: none"> <li>• Hep A/E, Norwalk, cholera, <i>Salmonella</i>, <i>Shigella</i>, <i>Giardia</i>, poliovirus, <i>Cryptosporidium</i>, <i>Cyclospora</i></li> </ul>

##### Environmental Exposures

Freshwater	<ul style="list-style-type: none"> <li>• <i>Leptospira</i> spp., schistosomes, <i>Acanthamoeba</i>, <i>Naegleria fowleri</i></li> </ul>
Soil	<ul style="list-style-type: none"> <li>• Hookworms, <i>Toxocara</i> spp. (visceral larva migrans), <i>Leptospira interrogans</i> (leptospirosis)</li> </ul>

Adapted with permission from *Lancet* 2003;361:1459-69

Table 23. Fever in the Returned Traveller

Illness	Geography/ Timing	Pathogen	Incubation Period	Clinical Manifestations	Diagnosis	Treatment
<b>Malaria</b>	Africa India C. and S. America SE Asia Usually rural, night-biting mosquitoes	<i>Plasmodium falciparum</i> <i>Plasmodium vivax</i> <i>P. malariae</i> <i>P. ovale</i> <i>P. knowlesi</i>	10 d to 40 yr	Fever and flu-like illness, (shaking chills, headache, muscle aches, and fatigue) Nausea, vomiting, and diarrhea Anemia and jaundice <i>Plasmodium falciparum</i> : (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure	Blood smear (thick and thin) x3 Antigen detection PCR (mostly a research tool)	Artesunate (for severe disease) + malarone, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine
<b>Dengue</b>	South East Asia Caribbean Usually urban, day-biting mosquitoes	Dengue viruses	3 d to 2 wk	Sudden onset of fever, headache, retro-orbital pain, myalgias and arthralgias Leukopenia Thrombocytopenia Hemorrhagic manifestations (rare in travelers)	Anti-dengue IgM positivity	Symptom relief: Acetaminophen (avoid using NSAIDs because of anticoagulant properties)
<b>Typhoid (enteric fever)</b>	Global but mostly Indian subcontinent	<i>Salmonella typhi</i> <i>Salmonella paratyphi</i>	3 to 60 d	Sustained fever 39° to 40° C (103° to 104° F) Abdominal pain, headache, loss of appetite, cough, constipation	Stool, urine or blood sample positive for <i>S. typhi</i> or <i>S. paratyphi</i>	Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone or macrolide
<b>Tick typhus</b>	Mediterranean South Africa India	<i>Rickettsia</i>	1 to 2 wk	Fever, headache, fatigue, muscle aches, occasionally rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes	Serology Presence of classic tick eschar	Doxycycline
<b>TB</b>	Global	<i>M. tuberculosis</i>	Variable	Fever, cough, hemoptysis	CXR Sputum culture and acid-fast stain	Ethambutol, isoniazid, pyrazinamide, rifampin
<b>Mononucleosis</b>	Caribbean, C. and S. America	EBV or CMV	30 to 50 d	Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly	Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test	Acetaminophen or NSAIDs, fluids

## Fever of Unknown Origin (FUO)



Table 24. Classification of Fever of Unknown Origin (FUO) – Temp &gt;38.3°C/101°F on several occasions

Classical FUO	Nosocomial FUO	Neutropenic FUO	HIV-associated FUO
Duration >3 wk	Hospitalized patient	Neutrophil count <500/mL or is expected to fall to that level in 1-2 d	HIV infections
Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation	Infection not present/ incubating on admission	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures	Duration >4 wk for outpatients, >3 d for hospitalized patients
	Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures		Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures



### Anti-Drugs that may Cause Fever:

- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimalarials)
- Anti-hypertensives (hydralazine, methyldopa)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arrhythmics (quinine, procainamide)
- Anti-inflammatories (NSAIDs)
- Anti-thrombotic (ASA)
- Anti-histamines
- Anti-thyroid

### Etiology of Classic FUO

- infectious causes (~30%)
  - TB: extra-pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvis, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - uncommon: viral (CMV, EBV), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin's) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - solid tumours: RCC (most common), also breast, liver (hepatoma), colon, pancreas or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still's disease
- miscellaneous (~20%)
  - drugs, factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- unknown despite investigations in 30-50% despite detailed work-up



### Causes of Nosocomial FUO

#### B, C, D, E

Bacterial and fungal infections of respiratory tract and surgical sites  
Catheters (intravascular and urinary)  
Drugs  
Emboli

### Approach to Classic FUO

- careful history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - bloodwork: CBC and differential, electrolytes, BUN, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis (SPEP), blood smear
  - cultures: blood (x 2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
  - serology: HIV, monospot, CMV IgM
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established
- if no diagnosis with the above, consider empiric therapy vs. watchful waiting
  - without intervention: patients that remain undiagnosed despite extensive work-up have good prognosis

## Infections in the Immunocompromised Host

- immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent
- type of immunosuppression predicts probable spectrum of agents

### Factors that Compromise the Immune System

- general: age (very young or elderly), malnutrition
- immune disease: HIV/AIDS, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

Table 25. Types of Immunocompromise

Type	Conditions	Vulnerable To
Cell-Mediated Immunity	HIV, Hodgkin's, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome	Latent viruses Fungi Parasites
Humoral Immunity	CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome	Encapsulated organisms ( <i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>N. meningitidis</i> , <i>Salmonella typhi</i> , GBS)
Neutrophil Function	Myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease	Catalase-producing organisms ( <i>Staphylococcus</i> , <i>Serratia</i> , <i>Nocardia</i> , <i>Aspergillus</i> )



#### Infections associated with Asplenia

- Hemophilus influenzae B*
- Streptococcus pneumoniae*
- Neisseria meningitidis*
- Salmonella*
- Babesiosis*
- Malaria*
- Capnocytophaga canimorsus* (dog bite)



ANC (absolute neutrophil count) = WBC x (%neutrophils + %bands)



Usual signs and symptoms of infection may be diminished because neutrophils are required for a robust inflammatory response. Exam and x-ray findings may be more subtle.



WBC is lowest between 5-10 d after last chemo cycle.



Prophylaxis against FN with G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) decreases hospitalization without affecting mortality (indicated if risk of FN 20% or if FN has occurred in a previous chemo cycle).

## Febrile Neutropenia (FN)

### Definition

- $\geq 38.3^{\circ}\text{C}/101^{\circ}\text{F}$  or  $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$  for  $\geq 1$  h) and one of:
  - ANC  $< 0.5$  OR
  - ANC  $< 1.0$  but trending down to 0.5

### Pathophysiology

- decreased neutrophil production
  - marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - iatrogenic: cancer chemotherapy, radiation, drugs
  - deficiencies: vitamin B<sub>12</sub>, folate
- increased peripheral neutrophil destruction
  - autoimmune: Felty's syndrome, SLE, antineutrophil antibodies
  - splenic sequestration

### Epidemiology/Etiology

- most common life-threatening complication of cancer therapy
- 8 cases per 1000 cancer patients per year in the US
- causative organism identified only 1/3 of the time
- GN (especially *Pseudomonas*) historically most common
- GP more common now
- fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially *Candida*, *Aspergillus*)

### Investigations

- examine for potential sites of infection: mucositis and line infections are most common
- do NOT perform DRE; examine perianal region
- blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports,  $\pm$  sputum C&S and NP swab for respiratory viruses
- CBC and differential, Cr, BUN, electrolytes, AST/ALT, total bilirubin

### Treatment

- most hospitals have their own specific protocol; one example is presented below

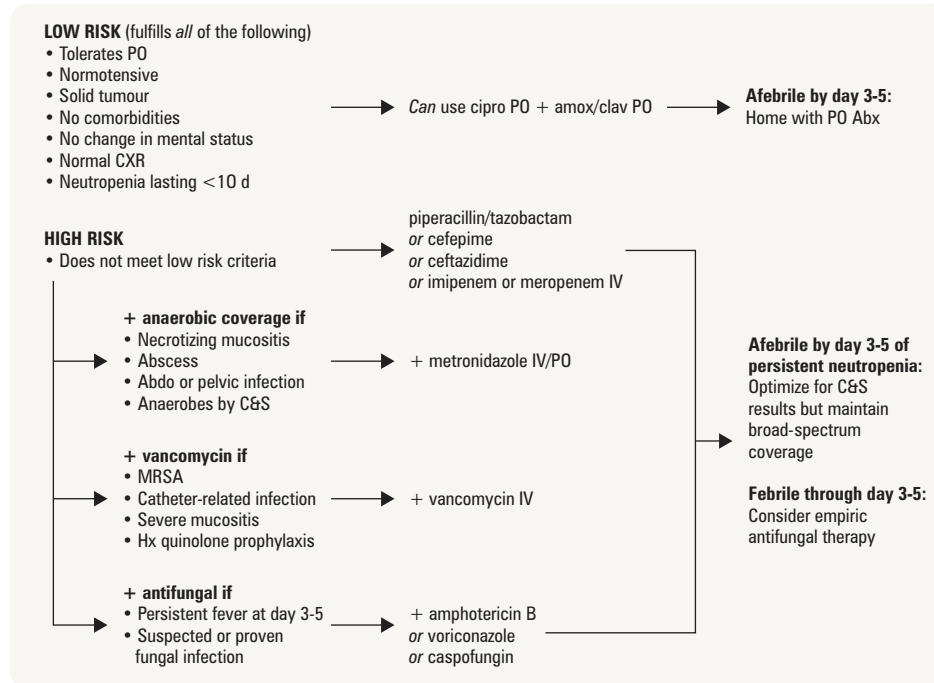


Figure 14. Example of treatment protocol for febrile neutropenia

## Infections in Solid Organ Transplant Recipients

- infection is a leading cause of early morbidity/mortality in transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 mo post-transplant:
  - bacterial infection of wound/lines/lungs, herpetic stomatitis
- common infections >1 mo post-transplant:
  - viral (especially CMV, EBV, VZV)
  - fungal (especially *Aspergillus*, *Cryptococcus*, *P. jiroveci*)
  - protozoan (especially *Toxoplasma*)
  - unusual bacterial/mycobacterial infections (especially TB, *Nocardia*, *Listeria*)

### Prophylactic Vaccinations Given Before Transplant

- to all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B vaccines
- if low titre or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 wk later)

## Immune Reconstitution Syndrome (IRS)

### Definition

- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

## Etiology

- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in HIV/AIDS or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation
- can occur in response to multiple infections:
  - *Mycobacteria* (*tuberculosis*, *avium* complex)
  - *Cryptococcus*
  - *Pneumocystis*
  - *Toxoplasma*
  - HBV and HCV
  - Herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - *Molluscum contagiosum*
- clinical features are dependent on the type and location of the pre-existing infection
- thought to be worse with quick increase in CD4 count and with lower pre-treatment CD4 count
- non-HIV conditions with documented IRS: solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

## Epidemiology

- in HIV patients starting HAART, IRS reported to affect ~10%

## Investigations

- IRS is a diagnosis of exclusion
- rule out drug reaction, patient non-adherence, drug resistance

## Treatment

- continue HAART therapy in HIV patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
- treat underlying infection; initiate treatment for some infections prior to HAART initiation
- consider starting corticosteroids/NSAIDs to decrease inflammatory response



HIV-1 is the predominant type in North America and most of the world.

HIV-2 is found mainly in West Africa.

Both lead to AIDS but HIV-2 is generally less virulent.



p24 = capsid protein

gp41 = fusion and entry

gp120 = attachment to host T cell



Homozygous CCR5 = immunity

Heterozygous CCR5 = slower course

# HIV and AIDS

## Epidemiology

### Canadian Situation (Public Health Agency of Canada, 2012)

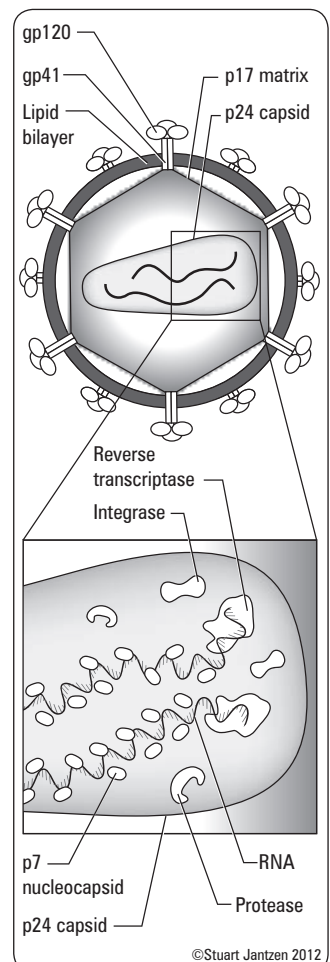
- estimated 71,300 Canadians living with HIV infection at the end of 2011, 25% unaware of HIV-positive status
- estimated 3,175 new infections occurred in 2011: MSM account for 47% of cases, IVDU 17%

### Global Situation (WHO Global Summary of the HIV/AIDS Epidemic, December 2010)

- estimated 34.0 million people living with HIV/AIDS in 2010
- estimated 2.7 million newly infected in 2010
- estimated 1.8 million AIDS-related deaths in 2010

## Definition and Pathophysiology

- human immunodeficiency virus (HIV) is a retrovirus that causes progressive immune system dysfunction which predisposes patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17) and capsid (p24) enclosing 2 single-stranded copies of RNA + enzymes in its core (see Figure 15)
- virion glycoproteins bind CD4 and CXCR4/CCR5 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by reverse transcriptase; dsDNA is integrated into host genome
- virus DNA transcribed during host replication and new virions are produced
- virions bud out of host cell, incorporating host cell membrane
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, increased cell turnover



©Stuart Jantzen 2012

Figure 15. HIV viral particle



Infection is NOT transmitted by casual contact, kissing, mosquitoes, toilet seats, shared utensils.

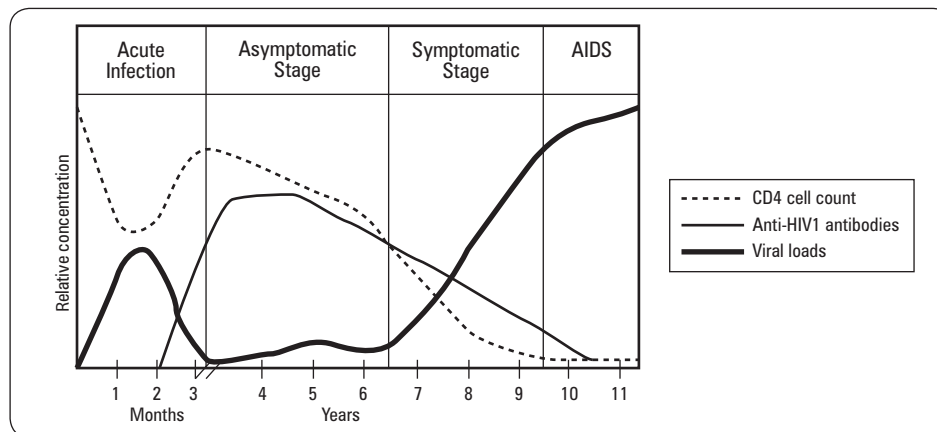
## Modes of Transmission

**Table 26. Modes of Transmission by Site and Medium**

HIV Invasion Site	Sub-location	Transmission Medium	Transmission Probability per Exposure Event
Female genital tract	Vagina, ectocervix, endocervix	Semen	1 in 200 to 1 in 2000
Male genital tract	Inner foreskin, penile urethra	Cervicovaginal and rectal secretions and desquamations	1 in 700 to 1 in 3000
Intestinal tract	Rectum Upper GI tract	Semen	1 in 20 to 1 in 300
		Semen	1 in 2500
		Maternal blood/genital secretions (intrapartum)	1 in 5 to 1 in 10
		Breastmilk	1 in 5 to 1 in 10
Placenta	Chorionic villi	Maternal blood (intrauterine)	1 in 10 to 1 in 20
Blood stream		Contaminated blood products	95 in 100
		Sharp/needlestick injuries	1 in 150

Adapted with permission from Macmillan Publishers Ltd. Nat Rev Immunology 2008;8:447-457.

## Natural History



**Figure 16. Relationships between CD4 T cell count, viral load, and anti-HIV antibodies**

### Acute (Infection) Retroviral Syndrome (ARS)

- 40-90% experience an acute "mononucleosis like" illness (fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, headaches, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high risk of transmission

### Asymptomatic (Latent) Stage

- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count: 500-1100 cells/mm<sup>3</sup>
- CD4 count drops 60-100 cells/mm<sup>3</sup> per year
- by 10 yr post-infection, 50% have AIDS, 30% demonstrate milder symptoms and <20% are asymptomatic if left untreated

### AIDS Definition in Canada

- HIV-positive AND
- one or more clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. PJP (previously PCP), esophageal candidiasis, CMV, MAC, TB, toxoplasmosis), malignancy (Kaposi's sarcoma, invasive cervical cancer), wasting syndrome OR
- first CD4 <200 (or <15%)



**Table 27. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)**

CD4 Counts	Possible Manifestations
<500 cells/mm <sup>3</sup>	Constitutional symptoms: fever, night sweats, fatigue, weight loss Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi's sarcoma (KS) Recurrent bacterial infections, especially pneumonia Pulmonary and extrapulmonary tuberculosis Lymphoma
<200 cells/mm <sup>3</sup>	<i>Pneumocystis jiroveci</i> pneumonia (formerly PCP) KS Oral thrush Local and/or disseminated fungal infections: <i>Cryptococcus neoformans</i> , <i>Coccidioides immitis</i> , <i>Histoplasma capsulatum</i>
<100 cells/mm <sup>3</sup>	Progressive multifocal leukoencephalopathy (PML) – JC virus CNS toxoplasmosis
<50 cells/mm <sup>3</sup>	CMV infection: retinitis, colitis, cholangiopathy, CNS disease Mycobacterium avium complex (MAC) Bacillary angiomatosis (disseminated <i>Bartonella</i> ) Primary central nervous system lymphoma (PCNSL)

## Laboratory Diagnosis

- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo
- initial screening test: enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%
  - some jurisdictions (e.g. Ontario) use combination Ag/Ab test as screen (tests for p24 antigen and HIV antibody)
- confirmatory test: if positive screen, Western blot confirmation by detection of antibodies to at least two different HIV protein bands (p24, gp41, gp120/160); specificity >99.99%
- rapid (point of care) antibody tests: higher false positives, therefore need to confirm positive results with traditional serology
- p24 antigen: detection by ELISA may be positive during "window period" before antibodies become detectable; combined with standard antibody test in some jurisdictions

## Management of the HIV-Positive Patient

- verify positive HIV test
- complete baseline history and physical examination, then follow-up every 3 mo
- laboratory evaluation
  - routine CD4 count to measure status of the immune system
  - routine HIV-RNA levels (viral load)
    - ♦ also important indicator of effect of anti-retroviral (ARV) therapy
  - baseline HIV resistance testing to guide ARV therapy
  - HLA-B\*5701 to reduce risk of abacavir hypersensitivity
  - baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
  - baseline serologies (hepatitis A, B and C, syphilis, toxoplasma, CMV, VZV)
  - routine biochemistry and hematology, CXR
  - annual fasting lipid profile and fasting glucose (due to HAART side effects)
- education
  - regular follow-up on CD4 counts and viral loads (q3-4mo) as well as strict adherence with ARVs improves prognosis
  - prevention of further transmission through safer sex and clean needles for injection drug use
  - HIV superinfection (transmission of different HIV strains from another HIV+ person) can rarely occur so barrier protection during sex is still recommended
- health care maintenance
  - assessment for counseling needs and referral for psychiatric or social concerns
  - vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative)
  - annual screening (PAP smear, STIs as applicable)
  - management of comorbid conditions (e.g. blood pressure monitoring, smoking cessation, alcohol/drug use)

**Table 28. Prophylaxis Against Opportunistic Infections in HIV-infected Patients**

Pathogen	Indication for Prophylaxis	Prophylactic Regimen
<i>Pneumocystis jiroveci</i>	CD4 count <200 cells/mm <sup>3</sup> or history of oral candidiasis	TMP-SMX 1 SS or DS OD
<i>Toxoplasma gondii</i>	IgG antibody to Toxoplasma and CD4 count <100 cells/mm <sup>3</sup>	As per prophylaxis for pneumocystis
<i>Mycobacterium tuberculosis</i>	PPD reaction >5 mm or contact with case of active TB	INH + pyridoxine daily x 9 mo
<i>Mycobacterium avium</i> complex	CD4 count <50 cells/mm <sup>3</sup>	Azithromycin 1200 mg q1wk

SS = single strength; DS = double strength

See 2002 USPHS/IDSA guidelines for preventing opportunistic infections among HIV-infected persons. Available from: <http://aidsinfo.nih.gov/>



**Seroconversion:** Development of detectable anti-HIV antibodies.

**Window Period:** Time between infection and development of anti-HIV antibodies; when serologic tests (ELISA, Western blot) are negative.



All infants born to HIV infected mothers have positive ELISA tests because of circulating maternal anti-HIV antibodies which disappear by 18 mo; early diagnosis is made by detection of HIV RNA in plasma.



### HIV Status

- CD4 count: progress and stage of disease
- Viral Load: rate of progression



1° and 2° prophylaxis may be discontinued if CD4 count is above threshold for ≥6 mo while on HAART.



### HLA-B\*5701 Testing

Abacavir hypersensitivity reactions usually only occur in individuals carrying this HLA allele (~5-7% of Caucasians, lower prevalence in other ethnic groups). Routine screening for HLA-B\*5701 prior to abacavir use.



### Reasons for Deterioration of a Patient with HIV/AIDS

- Opportunistic infections
- Neoplasms
- Medication-related toxicities
- Co-infections (e.g. HBV, HCV, STIs)
- Non-AIDS-related comorbidities (e.g. cardiovascular, renal, hepatic, neurocognitive, bone disease)

## Highly Active Antiretroviral Treatment (HAART)

### Overall Treatment Principles

- in asymptomatic patients: initiate HAART when CD4 <350; ongoing debate about when to initiate HAART when CD4 is between 350-500 or >500
  - current guidelines differ in various industrialized countries – see 2008 OARAC Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>
- other indications for initiating therapy include opportunistic infection/malignancy, pregnancy, HIV-associated nephropathy, HIV-associated thrombocytopenia, need for hepatitis B therapy in HBV co-infected patients
- consider starting treatment early if HCV co-infection, high HIV viral load, co-morbid conditions (e.g. cardiovascular disease)
- consider results of baseline resistance testing and complete ARV treatment history before (re-) initiating HAART
- goal: keep viral load <40 copies/mL; viral load should decrease 10-fold within 4-8 wk and be undetectable by 6 mo and restore immunological function
- secondary benefit of initiating therapy is 96% reduction in risk of transmitting HIV to sexual partners

### HAART Recommendations for Treatment of Naïve Patients

- 2 NRTIs + 1 NNRTI/PI (boosted with ritonavir)/INSTI

### Treatment Failure

- defined clinically (HIV progression), immunologically (failure to increase CD4 count by 25-50 over first year of treatment or CD4 decrease >100 over 1 yr), or virologically (failure to achieve viral load <40 copies/mL after 6 mo)
- ensure that viral load >40 is not just a transient viremia or 'blip'

**Table 29. Antiretroviral Drugs**

Class	Drugs	Mechanism	Adverse Effects
Nucleoside reverse transcriptase inhibitors (NRTIs)	zidovudine (AZT) lamivudine (3TC) stavudine (d4T) didanosine (ddI) abacavir (ABC) emtricitabine (FTC) <b>Combination Tablets:</b> AZT/3TC (Combivir®) AZT/3TC/ABC (Trizivir®) ABC/3TC (Kivexa®) TDF/FTC (Truvada®) tenofovir disoproxil fumarate (TDF)	Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth	Lactic acidosis Lipodystrophy Rash N/V/diarrhea Bone marrow suppression (AZT) Peripheral neuropathy (ddI, d4T) Drug-induced hypersensitivity (ABC) Pancreatitis (ddI/d4T) Myopathy (AZT)
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	efavirenz (EFZ) nevirapine (NVP) delavirdine (DLV) etravirine (ETR) rilpivirine (RPV)	Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication	Rash, Stevens-Johnson syndrome CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz) Hepatotoxicity (nevirapine – avoid in females with CD4 >250, men with CD4 >400) CYP3A4 interactions
Protease inhibitors (PIs)*	ritonavir (RTV) saquinavir (SQV) amprenavir (APV) nelfinavir (NFV) indinavir (IDV) atazanavir (ATV) fosamprenavir (FPV) lopinavir/ritonavir (Kaletra®) tipranavir (TPV) darunavir (DRV)	Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins	Lipodystrophy, metabolic syndrome N/V/diarrhea Nephrolithiasis (indinavir) Rash (APV) Hyperbilirubinemia (atazanavir, indinavir) CYP3A4 interactions Hyperlipidemia
Fusion inhibitor	enfuvirtide (T-20)	Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection	Injection site reactions, rash, infection, diarrhea, nausea, fatigue
CCR5 antagonist	maraviroc	Inhibit viral entry by blocking host CCR5 co-receptor	Fever, cough, dizziness
Integrase strand transfer inhibitors (INSTIs)	raltegravir elvitegravir	Inhibits integration of HIV DNA into the human genome thus preventing HIV replication	

\*Standard of care is to pharmacology boost most PIs with ritonavir to increase concentrations



#### SMART Study Group: CD4+ Count-Guided Interruption of Antiretroviral Treatment

*NEJM* 2006;355:2283-2296

**Rationale:** Given the viral resistance, drug toxicities, cost, and quality-of-life issues associated with lifelong ART, is there a difference between continuous and episodic therapy?

**Methods:** Persons with HIV with CD4+ count of <350 cc were randomly assigned to continuous ART [i.e. viral suppression (VS)] or episodic ART [i.e. drug conservation DC; deferral of therapy until CD4+ was <250 and use therapy until CD4+ count was <350]. Primary endpoint was development of an opportunistic disease or death from any cause. Secondary end point was major cardiovascular, renal, or hepatic disease.

**Results:** 5472 participants followed for 16 mo before protocol was modified for DC group. Opportunistic disease or death from any cause occurred in 120 and 47 participants in the DC and VS groups respectively (Hazard ratio 2.6; 95%CI 1.9 to 3.7; p<0.001). Hazard ratios for death from any cause and for major cardiovascular, renal, and hepatic disease were 1.8 (95%CI 1.2 to 2.9; p=0.007) and 1.7 (95%CI 1.1 to 2.5; p=0.009) respectively.

**Conclusions:** Episodic therapy significantly increased the risk of opportunistic disease or death from any cause and does not reduce the risk of adverse events that have been associated with ART, thus continuous therapy is recommended.



#### Treatment Failure

- Assess adherence
- Resistance testing
- Rule out opportunistic infections
- Rule out marrow suppression
- Construct new 3-drug regimen



#### Lactic Acidosis

- Occurs secondary to mitochondrial toxicity
- Symptoms include abdominal pain, fatigue, N/V, muscle weakness



#### Lipodystrophy

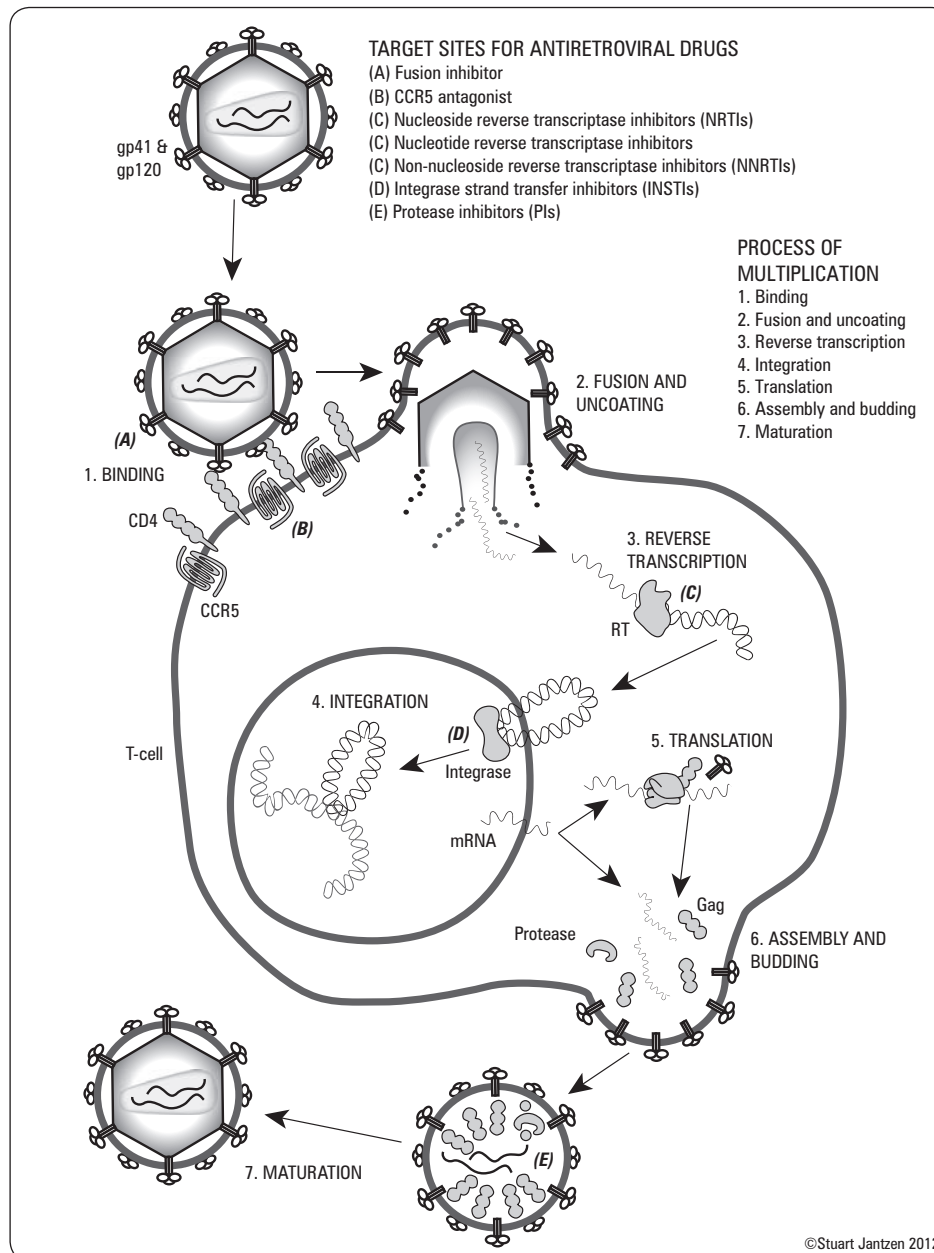
Body fat redistribution:

- Lipohypertrophy (e.g. dorsal fat pad, breast enlargement, increased abdominal girth) thought to be caused primarily by protease inhibitors
- Lipoatrophy (e.g. facial thinning, decreased adipose tissue in the extremities) is thought to be caused by thymidine analogue NRTIs such as ddI and AZT
- Metabolic abnormalities: lipids (increased LDL, increased TGs), glucose (insulin resistance, DM2), increased risk of CVD



#### Pharmacologic Boosting

- The goal of pharmacologic boosting is to increase the plasma exposure to the boosted drug
- PI boosting traditionally achieved by administering low-dose ritonavir along with the PI
- Ritonavir inhibits the metabolism of other PIs by inhibiting cytochrome P450 3A4 and p-glycoprotein, the enzyme systems responsible for metabolism of the PIs
- Cobicistat is a new non-ARV pharmacologic booster, presently co-formulate with the INSTI elvitegravir and alter to be co-formulated with some PIs



#### Tropism Testing

- In addition to CD4, HIV requires a co-receptor (either CCR5 or CXCR4) to enter cells
- CCR5 antagonists (e.g. Maraviroc) only work if virus is CCR5-tropic
- Tropism test required prior to initiating CCR5 antagonists

Figure 17. Mechanism of HIV replications

## Prevention of HIV Infection

- education, including harm-reduction:
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm prevention for injection drug users: avoid sharing needles
- treatment of HIV+ women with HAART during the 2nd and 3rd trimester of pregnancy and AZT during delivery followed by AZT treatment of the infant for 6 wk (decreases maternal-fetal transmission from 25% to <3%)
- universal blood and body precautions for health care workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV although additional data needed
- HAART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation

## Types of Testing

### 1. Nominal/name-based HIV testing

- the person ordering the test knows the identity of the person being tested for HIV
- the HIV test is ordered using the name of the person being tested
- person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
- the test result is recorded in the health care record of the person being tested

### 2. Non-nominal/non-identifying HIV testing

- similar to nominal/name-based testing on all points except:
  - the HIV test is ordered using a code or the initials of the person being tested

### 3. Anonymous testing

- available at specialized clinics
- the person ordering the HIV test does not know the identity of the person being tested
- the HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
- test results are not recorded on the health care record of the person being tested



Early identification of HIV is essential for patients to receive the maximal benefit from ARVs.

## HIV Pre- and Post-test Counselling

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV+ patients should be connected with local support services

## A Simplified Look at Antibiotics

- general overview, see Table 30 for more details

### 1. Penicillins (most *Streptococcus*, *N. meningitidis*, many oral anaerobes except *B. fragilis*)

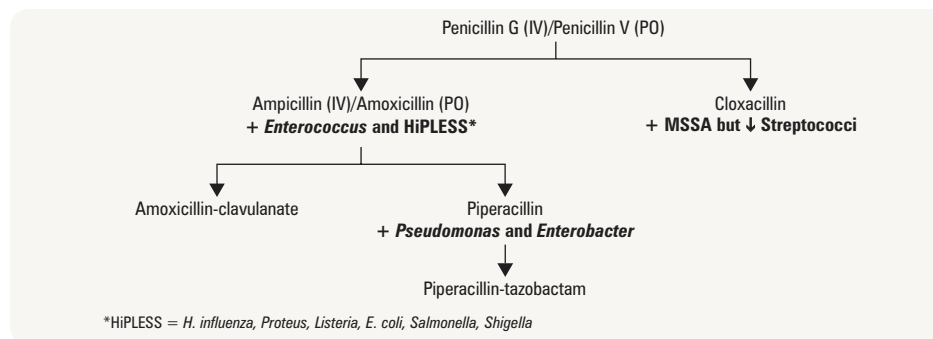


Figure 18. Penicillins

### 2. Cephalosporins (PO/IV)

- 1st generation: cephalexin/cefazolin (mostly GP, some GN)
- 2nd generation: cefuroxime/cefuroxime (some GP and some GN, \*anaerobes)
- 3rd generation: cefixime/cefotaxime, ceftriaxone (good *Streptococcal* coverage, mostly GN) and ceftazidime (no GP, mostly GN, *Pseudomonas*)
- 4th generation: --/cefepime (most GP, most GN, *Pseudomonas*)

### 3. Aminoglycosides (GN aerobic bacilli)

- gentamicin
- tobramycin
- amikacin

### 4. Macrolides [GP, *Hemophilus*, and atypical bacteria (*Legionella*, *Chlamydia*, *Mycoplasma*)]

- erythromycin
- clarithromycin
- azithromycin

**5. Fluoroquinolones (GN – although resistance becoming a huge problem)**

- ciprofloxacin (+ *Pseudomonas*)
- norfloxacin (for UTI only)
- respiratory fluoroquinolones (some GP, GN, "atypicals", *Legionella*, *Mycoplasma*, *Chlamydomphila*)
- levofloxacin
- moxifloxacin (+ anaerobes)

**6. Carbapenems (broad coverage: GP, GN and anaerobes)**

- imipenem (+ *Pseudomonas*)
- meropenem (+ *Pseudomonas*)
- ertapenem

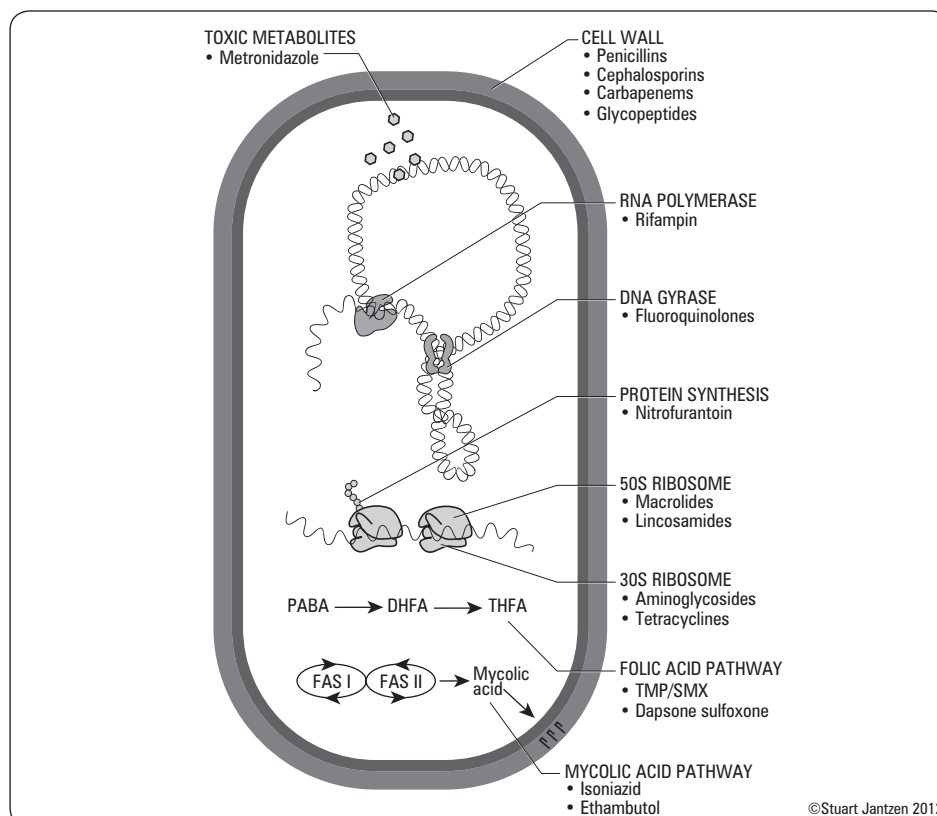
**7. Others**

- doxycycline/tetracycline (GP, syphilis, *Chlamydomphila*, *Rickettsia*, *Mycoplasma*)
- vancomycin (all GP and *C. difficile* – the oral form)
- linezolid (for resistant GP infections)
- clindamycin (most GP, GN anaerobes)
- TMP/SMX (most *S. aureus* incl. MRSA, GN aerobes, *Pneumocystis*)
- nitrofurantoin (GN bacilli, *S. saprophyticus*, *Enterococcus*)
- metronidazole (anaerobes incl. *C. difficile*; *Trichomonas*, *Entamoeba*)
- treatment for *C. Difficile*: metronidazole OR oral vancomycin; consider both in serious infection

## Antimicrobials

### Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S
    - ♦ if causative organism identified, use antibiotic to which organism is sensitive
    - ♦ if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)



**Figure 19. Mechanism of action of antibiotics**

**Reasons for Combination Therapy**

- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. *Enterococcus* spp. causing endocarditis)
- To prevent emergence of resistance



Bactericidal Antibiotics	Bacteriostatic Antibiotics
"Very Finely Proficient At CCCell Murder"	"ECSTaTiC"
Vancomycin	Erythromycin (and other macrolides)
Fluoroquinolones	Clindamycin
Penicillin	Sulfamethoxazole
Aminoglycosides	Trimethoprim
Cephalosporins	Tetracyclines
Carbapenems	Chloramphenicol
Metronidazole	

Table 30. Antibiotics

Class and Drugs		Coverage	Mechanism of Action		Adverse Effects	Indications	Contraindications
CELL WALL INHIBITORS							
Penicillins							
Benzyl penicillin - penicillin G IV/IM - penicillin V PO		GP <i>except Staphylococcus, Enterococcus</i> Oral anaerobes	Bactericidal: $\beta$ -lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan		Immediate allergy (IgE): anaphylaxis, urticaria Late-onset allergy (IgG): urticaria, rash, serum sickness Interstitial nephritis Dose related toxicity: seizures Diarrhea	Mild to moderately severe infections caused by susceptible organisms including actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis	Hypersensitivity to penicillin
Aminopenicillin - ampicillin IV - amoxicillin PO (Amoxil®)		Same as penicillin AND <i>Enterococcus</i> <i>Listeria</i>	See above		See above	Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (AOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for <i>H. pylori</i> treatment, Lyme disease, pneumococcal pneumonia; UTI (amoxicillin and ampicillin) for most enterococci and susceptible gram-negative pathogens	Hypersensitivity to penicillin or $\beta$ -lactam antibiotics
Isoxozoyl penicillin - cloxacillin - methicillin - nafcillin - oxacillin		Methicillin-sensitive <i>Staphylococcus aureus</i> ; streptococci	See above		See above	Bacterial infections caused by staphylococci and streptococci including skin soft-tissue infections	Hypersensitivity to cloxacillin or any penicillin
$\beta$ -lactam/ $\beta$ -lactamase Inhibitor combinations - amoxicillin clavulanate (Clavulin®, Augmentin®) - piperacillin/tazobactam (Tazocin®)		Same as penicillin AND <i>Staphylococcus</i> <i>H. influenzae</i> <i>Enterococcus</i> Anaerobes (oral and gut)	$\beta$ -lactamases produced by certain bacteria inactivate $\beta$ -lactams  Lactamase inhibitors prevent this process, preserving antibacterial effect of $\beta$ -lactams		See above	Various $\beta$ -lactamase producing bacteria, Clavulin® sensitive bacteria including RTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections	Hypersensitivity to penicillin or cephalosporin History of Clavulin®-associated jaundice or hepatic dysfunction
Cephalosporins							
PO 1° cephalexin (Keflex®)	IV cefazolin (Ancef®)	GP Good with the exception of <i>Enterococcus</i> and MRSA	GN <i>E. coli</i> , <i>Klebsiella</i> , <i>Proteus</i> , <i>H. influenzae</i> (not all isolates)	Bactericidal: $\beta$ -lactam inhibits PBP, prevents cross-linking of peptidoglycan, less susceptible to penicillinases	10% penicillin allergy cross-reactivity Nephrotoxicity	Skin and soft tissue infections, prevention of surgical site infections (cefazolin); infections caused by susceptible organisms (esp. <i>Staph.</i> and <i>Strep.</i> infections)	Hypersensitivity to cephalosporins or other $\beta$ -lactam antibiotic
2° cefuroxime (Ceftin®) cefprozil (Cefzil®)	cefuroxime (Zinacef®) cefoxitin <sup>A</sup>	Weaker activity than 1°	More coverage than 1° ( <sup>A</sup> includes anaerobes)	See above	See above	Upper and lower respiratory tract infections (there have been failures in bacteremia pneumococcal pneumonia; soft tissue	See above
3° cefixime (Suprax®)	ceftriaxone (Rocephin®) cefotaxime (Claforan®) ceftazidime <sup>B</sup> (Fortaz®)	<i>S. aureus</i> + <i>streptococcal</i> coverage (cefotaxime and ceftriaxone) especially <i>S. pneumoniae</i>	Broad coverage ( <sup>B</sup> includes <i>Pseudomonas</i> for ceftazidime only)	See above	~1% penicillin allergy cross-reactivity	Community-acquired pneumonia (cefotaxime, ceftriaxone), gonorrhea (use ceftriaxone), community-acquired bacterial meningitis (ceftriaxone, cefotaxime); abdominal and pelvic infections (cefotaxime or ceftriaxone in combination with metronidazole). Once-daily administration makes ceftriaxone convenient for outpatient IV therapy	Severe hypersensitivity (Type I) to other $\beta$ -lactam antibiotics
4°	cefepime (Maxipine®)	Broad spectrum	Broad coverage including <i>Pseudomonas</i>	See above	See above	Empiric therapy for febrile neutropenia	See above



Table 30. Antibiotics (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
<b>CELL WALL INHIBITORS</b>					
<b>Carbapenems</b>					
imipenem (Primaxin®)	GP except MRSA GN including <i>Pseudomonas</i> + <i>Enterobacter</i> , ESBLs, anaerobes	β-lactam inhibits PBP and prevents cross-linking of peptidoglycan	Penicillin allergy cross- reactivity Seizures	Treatment of infections caused by GNB producing extended- spectrum β-lactamases, serious infections caused by susceptible organisms	Hypersensitivity to imipenem
meropenem (Merrem®)	See above. Does not cover <i>Enterococcus</i> .	See above	See above	See above	Hypersensitivity to β-lactams
ertapenem (Invanz®)	GP except <i>Enterococcus</i> , MRSA GN including <i>Enterobacter</i> (but not <i>Pseudomonas</i> ), anaerobes	See above	See above	See above. Once-daily administration makes it convenient for outpatient IV therapy	Hypersensitivity to β-lactams
<b>Glycopeptides</b>					
Vancomycin (Vancocin®)	GP including MRSA, not VRE <i>C. difficile</i> if PO	Glycopeptide sterically inhibits cell wall synthesis	Red Man Syndrome Nephrotoxicity Ototoxicity Thrombocytopenia	Severe or life-threatening GP infections, patients with β-lactam allergy May only be taken orally for severe <i>C. difficile</i> infection	Hypersensitivity to vancomycin
<b>PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)</b>					
<b>Macrolides</b>					
erythromycin (Erybid®, Eryc®)	GP <u>except</u> <i>Enterococcus</i> GN: <i>Legionella</i> , <i>B. pertussis</i> "Atypicals": <i>Chlamydia</i> , <i>Mycoplasma</i>	Binds to 50S ribosomal subunit inhibiting protein synthesis	GI upset Acute cholestatic hepatitis Prolonged QT	Susceptible RTI, pertussis, diphtheria, Legionnaires' disease, skin and soft tissue infections	Hypersensitivity to erythromycin Concurrent therapy with astemizole, terfenadine
*This agent is rarely used due to GI upset					
clarithromycin (Biaxin®)	See above	See above	See above	Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for <i>H. pylori</i> treatment	Hypersensitivity to macrolides
azithromycin (Zithromax®)	See above	See above	See above	Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, <i>Campylobacter</i> infections if treatment indicated, chlamydia	Hypersensitivity to macrolides
<b>Lincosamides</b>					
clindamycin (Dalacin®)	GP <u>except</u> <i>Enterococcus</i> , most community-acquired MRSA Anaerobes	Inhibits peptide bond formation at 50S ribosome	Pseudomembranous colitis GI upset	Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections	Hypersensitivity to clindamycin Infants <30 d
chloramphenicol	GP GN Anaerobes	Inhibits peptidyl transferase action of tRNA at 50S ribosome	Aplastic anemia Grey Baby Syndrome	Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β-lactams	Hypersensitivity to chloramphenicol
linezolid (Zyvoxam®)	GP including VRE + MRSA	Binds 50S ribosome and prevents functional 70S initiation complex	HTN (acts as MAOI) Risks with prolonged use: myelosuppression optic neuropathy, peripheral neuropathy	Vancomycin-resistant <i>Enterococcus faecium</i> infections including intra-abdominal, skin and skin-structure, and urinary tract infections, MRSA infections as out patient therapy	Hypersensitivity to linezolid

**Table 30. Antibiotics** (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
<b>PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)</b>					
<b>Aminoglycosides</b>					
gentamicin tobramycin amikacin (Amikin®)	GN (includes <i>Pseudomonas</i> )	Binds 30S subunit of ribosome inhibiting protein synthesis	Nephrotoxicity (reversible) Vestibular and ototoxicity (irreversible). Vestibular toxicity is the most important aminoglycoside toxicity	GN infections when alternatives do not exist, UTIs, used in low doses for synergy with $\beta$ -lactams or with vancomycin for the treatment of serious enterococcal infections	Pre-existing hearing loss and renal dysfunction
<b>Tetracyclines</b>					
tetracycline (Apo-Tetra®, Nu-TetraT®) minocycline (MinocinT®) doxycycline (Doxycin®)	GP Anaerobes "Atypicals": <i>Chlamydomphila</i> , <i>Mycoplasma</i> , <i>Rickettsia</i> , <i>Borrelia burgdorferi</i> <i>Treponema</i> Malaria prophylaxis (doxycycline)	Binds 30S subunit of ribosome inhibiting protein synthesis	GI upset Hepatotoxicity Fanconi's syndrome Photosensitivity Teratogenic Yellow teeth and stunted bone growth in children	Rickettsial infections, <i>Chlamydomphila</i> , acne (tetracycline, minocycline), PID (step-down), malaria prophylaxis (doxycycline)	Severe renal or hepatic dysfunction Pregnancy or lactation Children under 8 yr
<b>TOPOISOMERASE INHIBITORS</b>					
<b>Fluoroquinolones (FQs)</b>					
ciprofloxacin (Cipro®) norfloxacin (Apo-Norfloxx®) ofloxacin (Floxin®) Respiratory FQs: levofloxacin (Levaquin®) moxifloxacin (Avelox®)	Poor GP activity GN (includes <i>Pseudomonas</i> ) Atypicals Moxifloxacin also covers many anaerobes	Inhibits DNA gyrase	H/A, dizziness Allergy Seizures Prolonged QT Dysglycemia (levofloxacin, moxifloxacin)	Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or ciprofloxacin in combination with amoxicillin/clavulanate low management of "low-risk" febrile neutropenia	
<b>Rifampin</b>	GP cocci <i>N. meningitidis</i> <i>H. influenza</i> <i>Mycobacteria</i>	Inhibits RNA polymerase	Hepatic dysfunction, P450 enzyme induction Orange tears/saliva/urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with <i>N. meningitidis</i> or HiB meningitis	Jaundice Not to be used as monotherapy (except for prophylaxis)
<b>Metronidazole</b> (Flagyl®)	Anaerobes Protozoa	Forms toxic metabolites in bacterial cell which damage microbial DNA	Disulfiram-type reaction with EtOH Seizures Peripheral neuropathy	Protozoal infections (trichomoniasis, <i>amebiasis</i> , <i>giardiasis</i> ), bacterial vaginosis, anaerobic bacterial infections	
<b>ANTI-METABOLITE</b>					
<b>Trimethoprim-Sulfamethoxazole (TMP/SMX)</b> (Septra®, Bactrim®)	GP, esp. <i>S. aureus</i> (incl. most MRSA) GN: enteric <i>Nocardia</i> Other: <i>Pneumocystis</i> , <i>Toxoplasmosis</i>	Inhibits folic acid pathway (TMP inhibits DHFR and SMX competes with PABA)	Hepatitis Stevens Johnson syndrome Bone marrow suppression Hyperkalemia Drug toxicity (increases free levels of many drugs, including glyburide, warfarin)	Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of <i>P. jiroveci</i> pneumonia	Hypersensitivity to TMP-SMX, sulfa drugs

**Table 30. Antibiotics** (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Indications	Contraindications
<b>ANTI-METABOLITE</b>					
<b>nitrofurantoin</b> (MacroBID®, (Macrochantin®))	<i>Enterococcus</i> , <i>S. saprophyticus</i> GN (coliforms)	Reactive metabolites inhibit ribosomal protein synthesis	Cholestasis, hepatitis Hemolysis if G6PD deficiency Interstitial lung disease with chronic use	Lower UTI; not pyelonephritis or bacteremia	Hypersensitivity to nitrofurantoin Anuria, oliguria or significant renal impairment Pregnant patients during labour and delivery or when labour imminent Infants < 1 mo of age
<b>ANTI-MYCOBACTERIALS</b>					
isoniazid (INH)	<i>Mycobacteria</i>	Inhibits mycolic acid synthesis	Hepatotoxicity Hepatitis Drug-induced SLE Peripheral neuropathy	Part of multidrug treatment for active TB, alone for treatment of latent TB	Drug-induced hepatitis or acute liver disease
rifampin (RIF)	<i>Mycobacteria</i>	Inhibits RNA polymerase	Hepatotoxicity P450 enzyme inducer Orange tears, saliva, urine	Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections	Jaundice Not to be used monotherapy (except for prophylaxis)
ethambutol	<i>Mycobacteria</i>	Inhibits mycolic acid synthesis	Loss of central and colour vision	Part of multidrug treatment for active TB and other mycobacterial infections	Renal failure
pyrazinamide (PZA)	<i>Mycobacteria</i>	Unknown	Hepatotoxicity Gout Gastric irritation	Part of multidrug treatment for active TB	Severe hepatic damage or acute liver disease Patients with acute gout
<b>SULFONES</b>					
dapsone sulfoxone	<i>M. Leprae</i> , part of treatment for <i>P. jiroveci</i> pneumonia (with TMP), <i>P. jiroveci</i> pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine	Inhibit folic acid synthesis by competition with PABA	Rash Drug fever Agranulocytosis		

**Table 31. Antibiotics for Selected Bacteria**

<i>Pseudomonas</i>	<i>S. aureus</i>	<i>Enterococcus</i>	<i>H. influenzae</i>	Anaerobes
ciprofloxacin	cloxacillin (MSSA)	ampicillin	amoxicillin-clavulanate	metronidazole
gentamicin, tobramycin	1° cephalosporin (MSSA)	amoxicillin	2°/3° cephalosporin	clindamycin
piperacillin/tazobactam	clindamycin	vancomycin	macrolides (clarithromycin, azithromycin)	amoxicillin- clavulanate
ceftazidime	vancomycin (incl. MRSA)	nitrofurantoin (lower UTI)	levofloxacin	cefoxitin
cefepime	linezolid (incl. MRSA)	linezolid for VRE	moxifloxacin	piperacillin-tazobactam
meropenem	daptomycin (incl. MRSA)	daptomycin for VRE		moxifloxacin
imipenem		tigecycline for VRE		ertapenem, imipenem, meropenem

**Rifampin**

- Good adjunct for treating prosthetic device infection (bacterial biofilm)
- Always used in combination with other antibiotics to reduce emergence of resistance

## Antivirals

**Table 32. Antivirals**

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
<b>ANTI-HERPESVIRUS</b>				
acyclovir valacyclovir (ValtrexT®) (prodrug of acyclovir)	HSV-1,2 VZV	Guanosine analog inhibits viral DNA polymerase	PO well-tolerated IV: nephrotoxicity, CNS	Hypersensitivity to acyclovir or valacyclovir
famciclovir (Famvir®) penciclovir	HSV-1,2 VZV	See above	H/A, nausea	Hypersensitivity to famciclovir or penciclovir
ganciclovir (Cytovene®) valganciclovir (prodrug of ganciclovir)	CMV HSV-1,2, VZV	See above	Heme: neutropenia, thrombocytopenia, anemia GI: N/V, diarrhea	Hypersensitivity to ganciclovir or valganciclovir Possible cross-hypersensitivity between acyclovir and valacyclovir
foscarnet	CMV Acyclovir-resistant HSV, VZV	Pyrophosphate analog inhibits viral DNA polymerase	Nephrotoxicity (reversible) Anemia, electrolyte disturbances	

Table 32. Antivirals (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
OTHER ANTIVIRALS				
interferon-PEG interferon-α 2a, 2b	Chronic hep B, hep C HPV	Inhibits viral protein synthesis	"Flu-like" syndrome Depression Bone marrow suppression	Hypersensitivity to any interferon Cannot use in combination with ribavirin if renal impairment
ribavirin (Virazole®)	Chronic hep C RSV Lassa fever	Guanosine analog with multiple postulated mechanisms of action	Hemolytic anemia Rash, conjunctivitis Highly teratogenic	Pregnancy or women who may become pregnant
lamivudine (3TC®, Heptovir®)	Chronic hep B HIV	See HIV/AIDS, ID41		Hypersensitivity to lamivudine
M2 inhibitors: amantadine (Endantadine®, Symmetrel®) rimantadine	Influenza A treatment	Inhibits viral uncoating after infection of cell	Anti-cholinergic effects CNS: anxiety, insomnia, H/A, dizziness, difficulty concentrating	
Neuraminidase inhibitors: zanamavir (Relenza®) oseltamavir (Tamiflu®)	Influenza A and B: treatment and prophylaxis	Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation	GI: N/V, diarrhea Bronchospasm in zanamavir	

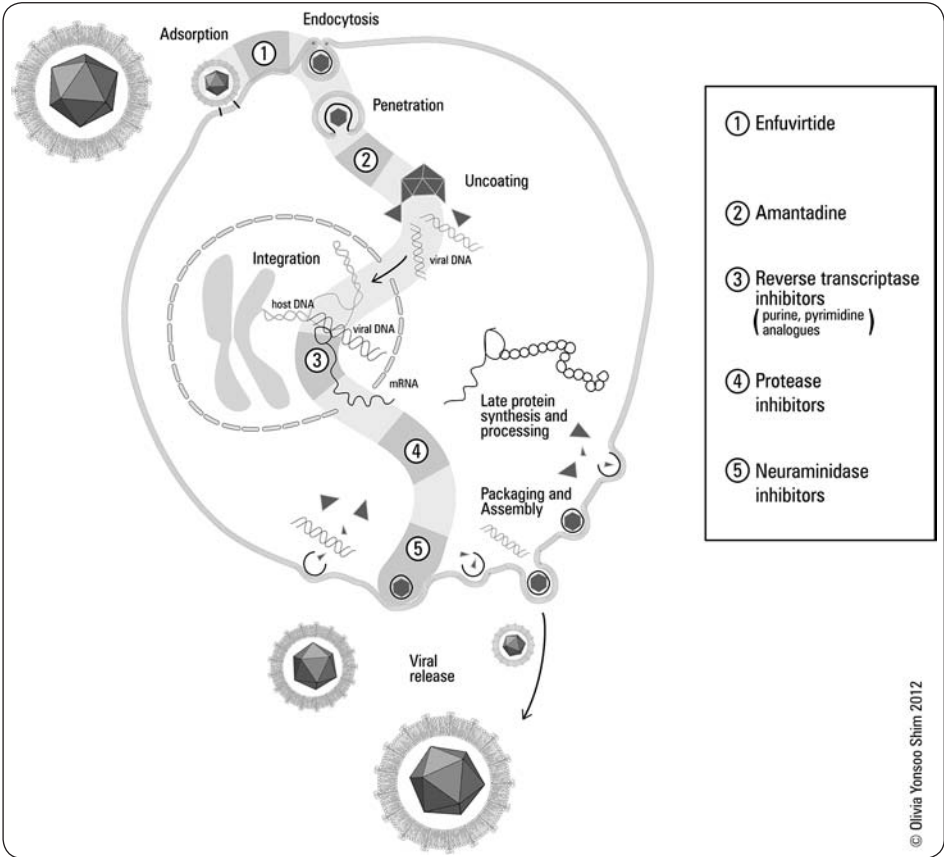


Figure 20. Mechanism of action of antivirals

# Antifungals

Table 33. Antifungals

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
<b>POLYENES</b>				
amphotericin B	Endemic mycoses: Histoplasmosis, blastomycosis, coccidiomycosis Pulmonary: Aspergillosis CNS: Cryptococcus	A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death	Nephrotoxicity Hypo/hyperkalemia Infusion reactions: chills, fevers, H/A Peripheral phlebitis	Renal impairment
nystatin (oral, topical)	Candidiasis: mucocutaneous, GI, oral (thrush), vaginal	See above Not absorbed from the GI tract	GI: N/V, diarrhea Highly toxic if given IV	
<b>IMIDAZOLES</b>				
clotrimazole (Canesten®)	Oral and vulvovaginal candidiasis Dermatomycoses	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Pruritis, skin irritation	
miconazole (Monistat®, Micozole®)	Vulvovaginal candidiasis Dermatomycoses		Vaginal burning Nausea and vomiting	
ketoconazole (Nizoral®)	Dermatomycoses Seborrheic dermatitis		Pruritis, skin irritation GI nonspecific Results in decreased androgen and testosterone synthesis	Cross-sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant
<b>TRIAZOLES</b>				
fluconazole (Diflucan®)	Candida infections (mucosal and invasive) Cryptococcal meningitis (step-down therapy)	All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability	Elevated liver enzymes GI nonspecific	Cross-sensitivity with other azoles unknown Concurrent use of terfenadine if dose of fluconazole >400 mg
itraconazole (Sporanox®)	Porotrichosis Onychomycoses Endemic mycoses: Histoplasmosis, blastomycosis, coccidiomycosis		Elevated liver enzymes Rash GI nonspecific	Cross-sensitivity with other azoles unknown Severe ventricular dysfunction
voriconazole (Vfend®)	Aspergillosis Candidiasis		Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma long-term use in immunosuppressed patients	Cross-sensitivity with other azoles unknown May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids
posaconazole (Posanol®, Noxafil®)	Candidiasis Aspergillosis Mucormycosis		GI nonspecific Elevated liver enzymes Headache	Coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus
<b>ALLYLAMINES</b>				
terbinafine (Lamisil®)	Dermatomycoses Onychomycoses	Inhibits enzyme needed for ergosterol synthesis	Rash, local irritation GI nonspecific, transaminitis	Active liver disease
<b>ECHINOCANDINS</b>				
caspofungin micafungin anidulafungin	Refractory aspergillosis, candidemia (azole- resistant)	Inhibits 1-3 $\beta$ -glycan synthesis (needed for fungal cell wall)	Hepatotoxicity	

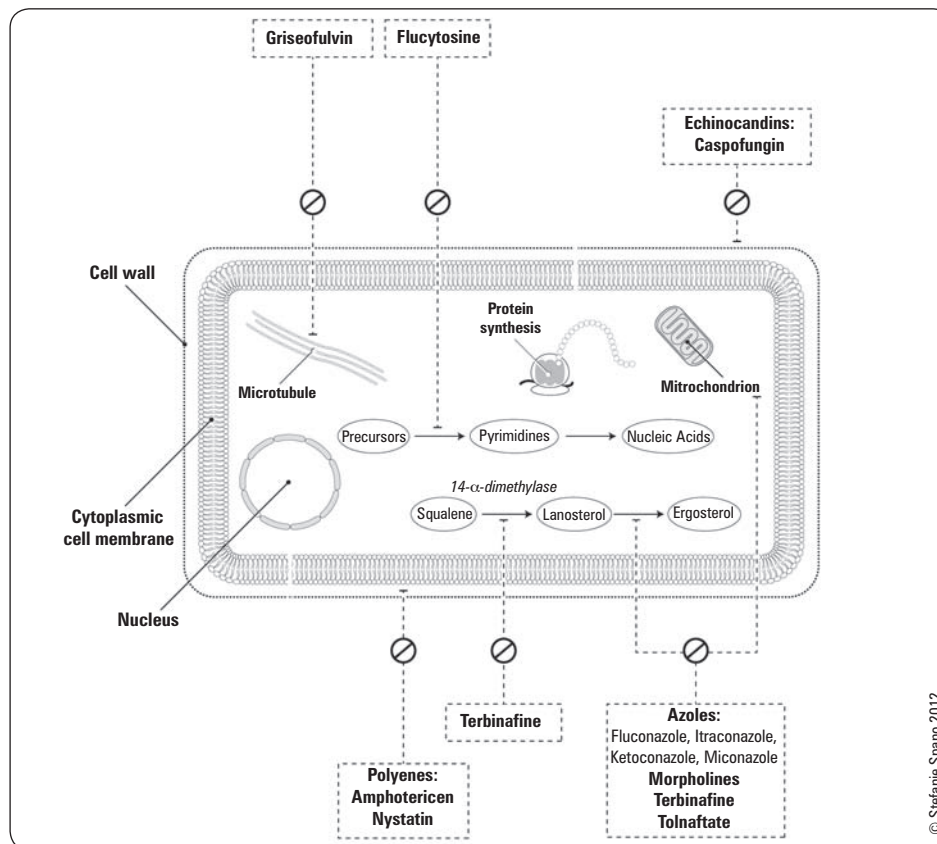


Figure 21. Mechanism of action of antifungals

## Antiparasitics

Table 34. Antiparasitics

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
<b>ANTIMALARIALS</b>				
chloroquine	Malaria: treatment of erythrocytic phase of all five species of <i>Plasmodium</i> that infect humans Note: High resistance of <i>P. falciparum</i> and <i>P. vivax</i> in certain geographic areas	Inhibits parasite heme polymerase	CNS: blurred vision, retinopathy, dizziness Nonspecific GI (rare with prophylaxis)	Hypersensitivity to chloroquine or other 4-aminoquinoline Retinal or visual field changes due to 4-aminoquinoline
quinine	Malaria: treatment of all five species of <i>Plasmodium</i> that infect humans, including chloroquine-resistant <i>P. falciparum</i>		Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (N/V, diarrhea), CNS (H/A, fever) Hypoglycemia	Hypersensitivity to quinine, may have cross-sensitivity with quinidine Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use
mefloquine (Lariam®)	Malaria: treatment and prophylaxis of all four species of <i>Plasmodium</i> that infect humans		CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, H/A	History of seizures, psychosis, severe anxiety or depression
primaquine	Malaria: treatment of liver hypnozoites of <i>P. vivax</i> and <i>P. ovale</i> . Prophylaxis of all <i>Plasmodium</i> spp. <i>Pneumocystis jiroveci</i> (with clindamycin)	Interferes with mitochondrial function	Hemolytic anemia in G6PD deficient GI upset (take with food)	GI nonspecific G6PD deficiency Concurrent or recent use of quinacrine Pregnancy
atovaquone/proguanil (Malarone®)	Malaria: treatment and prophylaxis of <i>P. falciparum</i>	Inhibits mitochondrial electron transport and dihydrofolate reductase	N/V, anorexia, diarrhea, abdo pain (take with food)	Hypersensitivity to atovaquone or proguanil Severe renal impairment
artemisinin derivatives (artemeter, artesunate, etc.) Note: marketed primarily in endemic countries	Malaria: treatment of all <i>Plasmodium</i> species Severe malaria (IV artesunate) Typically used in combination with a longer-acting agent from above	Binds iron, leading to formation of free radicals that damage parasite proteins	Transient neurologic deficits (nystagmus, balance disturbance) Transient neuropenia (at high doses of oral artesunate)	Hypersensitivity to artemisinins



Table 34. Antiparasitics (continued)

Class and Drugs	Coverage	Mechanism of Action	Adverse Effects	Contraindications
<b>OTHER ANTI-PROTOZOAL</b>				
iodoquinol (Diodoquin®)	Amebiasis: <i>E. histolytica</i> , <i>Dientamoeba fragilis</i> , <i>Balantidium coli</i> , <i>Blastocystis hominis</i>	Contact amoebicide that acts in intestinal lumen by uncertain mechanism	GI: N/V, diarrhea, abdo pain CNS: H/A, seizures, encephalitis	Hypersensitivity to any 8-hydroxy-quinoline or iodine Patients with hepatic damage or optic neuropathy Pregnancy
metronidazole	Amebiasis, <i>T. vaginalis</i> , giardiasis	See <i>Antibiotics</i> , ID47		
nitazoxanide	<i>Cryptosporidium</i> , giardiasis	Interferes with parasite anaerobic metabolism	N/V, diarrhea, abdo pain, headache	Hypersensitivity to nitazoxanide
<b>ANTI-HELMINTHICS</b>				
praziquantel	<i>Schistosomiasis</i> and other flukes Tapeworms	Increases Ca <sup>2+</sup> permeability of helminth cell membrane, causing paralysis and detachment	N/V, fever, dizziness	Ocular cysticercosis
albendazole	Intestinal roundworms <i>Neurocysticercosis</i> <i>Microsporidiosis</i> <i>Echinococcus</i> → Hydatid disease	Inhibits glucose uptake into susceptible parasites	Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis	Pregnancy Ocular cysticercosis or intraventricular cysticercosis
mebendazole (Vermox®)	Intestinal roundworms: - pinworm - whipworm - hookworm - roundworm (e.g. <i>Ascaris</i> )	Inhibits microtubule formation and glucose uptake	Nonspecific GI	Pregnancy, infants
ivermectin	<i>Strongyloidiasis</i> <i>Onchocerciasis</i> Scabies	Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis	Nausea, bloating, diarrhea, myalgias, lightheadedness, headache	Hypersensitivity to ivermectin Pregnancy
diethylcarbamazine	<i>Wuchereria bancrofti</i> <i>Loa loa</i>		Anorexia, N/V, headache, drowsiness, encephalitis, retinal hemorrhage Mazzotti reaction if coinfectd with onchocerciasis	Pregnancy

## Quick Reference: Common Infections and their Antibiotic Management

Table 35. Common Infections and their Empiric Antibiotic Management

Infection	Bacteria	Antibiotic
<b>RESPIRATORY</b>		
<b>Pneumonia</b>		
• Community-acquired	<i>S. pneumoniae</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>Mycoplasma</i> , <i>Chlamydia</i> , <i>Legionella</i> , <i>S. aureus</i>	Outpatient: amoxicillin-clavulanate OR doxycycline Hospitalized: antipseudomonal respiratory fluoroquinolone OR 3rd generation cephalosporin ± macrolide
• Hospital-acquired:	GNR (including <i>Pseudomonas</i> in special settings such as ICU)	ceftriaxone (if not at risk for <i>Pseudomonas</i> ) OR pip/tazo OR meropenem
<b>Tuberculosis</b>	<i>Mycobacterium tuberculosis</i>	isoniazid + rifampin + pyrazinamide + ethambutol + pyridoxine (for initial empiric therapy)
<b>UTI</b>		
<b>Cystitis</b>	KEEP <sup>2</sup> S	fluoroquinolone OR TMP/SMX OR nitrofurantoin
<b>Pyelonephritis</b>	KEEP <sup>2</sup> S	ciprofloxacin OR 3rd gen. cep
<b>Urethritis</b>	<i>Neisseria gonorrhoea</i> <i>Chlamydia</i>	ceftriaxone azithromycin OR doxycycline
<b>SOFT TISSUE</b>		
<b>Cellulitis</b>	β-hemolytic streptococci, MSSA	cephalexin OR cefazolin
<b>Necrotizing Fasciitis</b>	Type I: polymicrobial (GNR and anaerobes)	pip/tazo + clindamycin
	Type II: β-hemolytic streptococci Unknown organism	penicillin G + clindamycin

KEEP<sup>2</sup>S = *Klebsiella*, *E. Coli*, *Enterococci*, *Proteus mirabilis*, *Pseudomonas*, *S. saprophyticus*

**Table 35. Common Infections and their Empiric Antibiotic Management (continued)**

Infection	Bacteria	Antibiotic
<b>BONE</b>		
<b>Osteomyelitis</b>	MSSA	cloxacillin OR cefazolin
<b>Diabetic Foot</b>		
	• Mild	MSSA, <i>Streptococcus</i> spp.
• Moderate or severe	polymicrobial	cephalexin OR clindamycin clindamycin + ciprofloxacin OR pip/tazo ± vancomycin if MRSA suspected
<b>Septic Arthritis</b>	<i>N. gonorrhoeae</i> (sexually active adults) <i>S. aureus</i> , <i>S. pyogenes</i>	vancomycin + ceftriaxone
<b>OTHER</b>		
<b>Meningitis</b>	<i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>H. influenza</i>	ceftriaxone + vancomycin (+ ampicillin for <i>Listeria</i> in very young, old, immunocompromised)
<b>Bacterial Endocarditis</b>		
• Native valve	<i>S. viridans</i> , <i>S. aureus</i> , <i>Enterococcus</i>	Usually non urgent and can wait for confirmation of etiology Empiric therapy if patient unstable, vancomycin and gentamicin or ceftriaxone. Take multiple blood cultures prior to initiating therapy

## References

### Principles of Microbiology

Andreoli TE. Cecil essentials of medicine, 6th ed. WB Saunders, 2003.  
Hawley LB. High yield microbiology and infectious diseases. Lippincott Williams & Wilkins, 2000.  
Mandell GL, Mandell, Douglas, and Bennett's principles and practice of infectious disease, 6th ed. Churchill Livingstone, 2005.  
Levinson W, Jawetz E. Medical microbiology and immunology: examination and board review, 7th ed. McGraw Hill, 2003.  
McGraw Hill. Harrison's Online (internet). Available from: <http://www.harrissononline.com>.  
Schaechter M, Engleberg N, Eisenstein B, Medoff G. Mechanisms of microbial disease. Lippincott Williams & Wilkins, 1998.

### Neurological Infections

Bloch KC, Glaser C. Diagnostic approaches for patients with suspected encephalitis. Curr Infect Dis Reports 2007;9:315-322.  
Peterson LR, et al. West Nile virus. JAMA 2003;290:524-527.  
Roberts L. Mosquitos and disease. Science 2002;298:82-83.  
Rupprecht CE, Hanlon CA, Hemachudha T. Rabies re-examined. Lancet Infect Dis 2002;2:327-343.  
Rupprecht CE, Gibbons RV. Prophylaxis against rabies. NEJM 2004;351:2626-2635.

### Respiratory Infections

Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003;37:752-760.  
Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America / American Thoracic Society Consensus guidelines on the management of community-acquired pneumonia in adults. CID 2007;44(Suppl 2):S27-S72.  
H1N1 Flu Vaccine Information. Public Health Agency of Canada. (accessed June 6, 2011). Available from: <http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/monovacc/index-eng.php>.  
H1N1 Flu. Centers for Disease Control and Prevention, 2009. (accessed June 6, 2011). Available from: <http://www.cdc.gov/h1n1flu/>.

### Cardiac Infections

Baddour M, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. Circulation 2005;111:e394-e434.  
Li JS, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-638.  
Wilson W, et al. Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 2007;116:1736-1754.

### Gastrointestinal Infections

Pickering LK, Baker CJ, Long SS, McMillan JA, (editors). Red book: 2006 Report of the committee on infectious diseases, 27th ed. Elk Grove Village: American Academy of Pediatrics, 2006.  
Gottlieb T, Heather CS. Diarrhoea in adults (acute). Clinical Evidence 2011;02:901.  
Thielman NM, Guerrant RL. Acute infectious diarrhea. NEJM 2004;350:38-47.  
Dupont HL. Bacterial diarrhea. NEJM 2009;361:1560-1569  
Jelinek T, Kollaritsch H. Vaccination with Dukoral sup.[R] against travelers' diarrhea (ETEC) and cholera. Expert review of vaccines 7.5 (2008): 561+. Expanded Academic ASAP. Web. 17 Apr. 2011.  
Travelers' Diarrhea (Internet). Atlanta: Centers for Disease Control and Prevention; 2006 Nov 21. Available from: <http://www.cdc.gov>.

### Bone and Joint Infections

Butalia S, Palda VA, Sargeant RJ, Detsky AS, Mourad O. Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA 2008;299:806-813.  
Hellman DB, Imboden JB. Current medical diagnosis and treatment. 2010. Edited by McPhee SJ, Papadakis MA. McGraw-Hill, 2010. Musculoskeletal and Immunologic disorders.  
Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. The Sanford guide to antimicrobial therapy, 38th ed. 2008.  
Margaretten ME, Kohlswes J, Moore D, Bent S. Does this adult patient have septic arthritis? JAMA 2007;297:1478-1488.

### Systemic Infections

Alejandria MM, Lansang MA, Dans LF, Mantaring JBV. Intravenous immunoglobulin for treating sepsis and septic shock (Cochrane Review). In: The Cochrane Library, Issue 2, 2002. Oxford: Update Software.  
American College of Chest Physicians/Society of Critical Care Medicine Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. SO – Crit Care Med. 1992;20:864-874.  
Bernard GR, Vincent JL, LaTerre PF, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. NEJM. 2001;344:699-709.  
Fournier F, Chopin C, Goumand J, et al. Septic shock, multiple organ failure, and disseminated intravascular coagulation: compared patterns of antithrombin III, protein C and protein S deficiencies. Chest. 1992;101:816-823.  
Smieja MJ, Marchetti CA, Cook DJ, Smail FM (2002). Isoniazid for preventing tuberculosis in non-HIV infected persons (Cochrane Review). In: The Cochrane Library, Issue 2. Oxford: Update Software.  
Steere AC. Lyme disease. NEJM.2001;345:115-125.  
Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection Am J Respir Crit Care Med 2000;161:S221-247.  
Tuberculosis: selected series. Mechanisms of microbial disease. CMAJ 1999. p160.  
Public Health Agency of Canada. Canadian tuberculosis standards, 6th ed. 2007.

**HIV and AIDS**

Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, 2006. Available from: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf>.  
Guidelines for preventing opportunistic infections among HIV-infected persons – 2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. Available from: <http://aidsinfo.nih.gov/ContentFiles/OIpreventionGL.pdf>.  
Hammer SM, Saag MS, Schechter, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society: USA panel. *JAMA* 2006; 296:827-43.  
Hladik F and McElrath MJ. Setting the stage: host invasion by HIV. *Nat Rev Immunol* 2008;8:447-457.  
Moylett EH and Shearer WT. HIV: clinical manifestations. *J Allergy Clin Immunol* 2002;110:3-16.  
Public Health Agency of Canada. HIV and AIDS in Canada. Summary: estimates of HIV prevalence and incidence in Canada, 2008. Ottawa: PHAC, 2009:1-3. Available from: <http://www.phac-aspc.gc.ca/aids-sida/publication/index.html#surveillance>.  
WHO. AIDS epidemic update 2009. Available from: [http://data.unaids.org/pub/EPISlides/2009/2009\\_epiupdate\\_en.pdf](http://data.unaids.org/pub/EPISlides/2009/2009_epiupdate_en.pdf).  
WHO Case definitions of HIV for surveillance and revised clinical staging and Immunological classification of HIV-related disease in adults and children, 2006. (accessed June 6, 2011.) Available from: <http://www.who.int/hiv/pub/vct/hivstaging/en/index.html>.  
Wilkinson D. Drugs for preventing tuberculosis in HIV infected persons (Cochrane Review). The Cochrane Library 2002;Issue 2. Oxford: Update Software.

**Fungal Infections**

Catherine E, et al. *Pneumocystis jirovecii* pneumonia. *Infect Dis Clin North Am* 2010;24:107-138.  
Bope ET, Kellerman R, Rakel RE. *Bope: Conn's current therapy*, 1st ed. Elsevier, 2011.  
Hustan SM, Mody CH. *Cryptococcus: an emerging respiratory mycosis*. *Clin Chest Med* 2009;30:253-264.  
Habif TP. *Clinical dermatology*, 5th ed. Elsevier Inc. Mosby, 2009.  
Mandell, Douglas and Benetts principles and practice of infectious diseases, 7th ed. Churchill Livingstone, 2009.  
Pappas PG, et al. Clinical practice guidelines for the management of candidiasis. *Clin Infect Dis* 2009;48:503-535.

**Parasitic Infections**

Center for Disease Control and Prevention. DPDX: identification and diagnosis of parasites of public health concern. Available from: <http://www.dpd.cdc.gov/dpdx/Default.htm>.  
Croft MA, Jacquerioz FA. Drugs for preventing malaria in travelers. *Cochrane DB Syst Rev* 2009;4:CD006491.

**Infections in the Immunocompromised Host**

Hughes WT, et al. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *CID* 2002;34:731-757.  
Freifeld AG, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011;52:e56-e93.

**Fever of Unknown Origin**

Kncokaert DC, et al. Fever of unknown Origin in adults: 40 years on. *J Internal Med* 2003;253:263-275.  
Spira AM. Assessment of traveller's who return home ill. *Lancet* 2003;361:1459-1469.

**Nosocomial Infections**

Antibiotic Subcommittee of the Pharmacy and Therapeutics Committee. Guidelines for antimicrobial use. University Health Network, 2009.  
Pickering LK, Baker CJ, Long SS, McMillan JA, (editors). *Red book: 2006 report of the committee on infectious diseases*, 27th ed. Elk Grove Village: American Academy of Pediatrics, 2006. *Staphylococcal infections*.  
Simor AE, Ofner-Agostini M, Gravel D, et al. Surveillance for methicillin-resistant *Staphylococcus aureus* in canadian hospitals – a report update from the Canadian Nosocomial Infection Surveillance Program. *CCDR* 2005;31(3):1-7.  
Simor AE, Phillips E, McGeer A, et al. Randomized controlled trial of chlorhexidine gluconate for washing, intranasal mupirocin, and rifampin and doxycycline versus no treatment for the eradication of methicillin-resistant *Staphylococcus aureus* colonization. *Clin Infect Dis* 2007;44:178-185.

**Travel Medicine**

Boggild A, Ghesquiere W, McCarthy A. Fever in the returning international traveller initial assessment guidelines. *Can Comm Dis Report* 2011;37:1-15.  
Freedman DO, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *NEJM* 2006;354:119-1130.  
Luzuriaga K, Sullivan J. Infectious mononucleosis. *NEJM* 2010;362:1993-2000.  
Ryan ET, Wilson ME, Kain KC. Illness after international travel. *NEJM* 2002;347:505-16.  
Re VL and Gluckman SJ. Fever in the returned traveler. *Am Fam Physician* 2003;68:1343-50.  
Spira AM. Assessment of travellers who return home ill. *Lancet* 2003;361:1459-69.

**Antimicrobials**

e-CPS. Canadian Pharmacists Association, 2008. Available from: <http://e-cps.pharmacists.ca>.  
MD consult drugs online (internet). Available from: <http://home.mdconsult.com/das/drugs/>.  
Schlossberg D, (editor). *Current therapy of infectious disease*, 2nd ed. St Louis: Mosby, 2001.

**Antivirals**

Mandell, Douglas, Bennett. *Principles and practice of infectious diseases*, 7th ed. Churchill Livingstone, 2009.  
Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *NEJM* 2006;355:2283-2296.

Ashley Leckie, Laura Quigley and Erin Wong, chapter editors  
 Maria Jogova and Howard Meng, associate editors  
 Melini Gupta, EBM editor  
 Dr. Taebong Chung, Dr. Nasir Jaffer and Dr. Eugene Yu, staff editors

<b>Imaging Modalities</b> . . . . .	<b>2</b>	<b>Musculoskeletal System (MSK)</b> . . . . .	<b>22</b>
Ultrasound (U/S)		Modalities	
Magnetic Resonance Imaging (MRI)		Approach to Interpretation of Bone X-Rays	
Positron Emission Tomography Scans (PET)		Trauma	
Contrast Enhancement		Arthritis	
		Bone Tumour	
		Infection	
		Metabolic Bone Disease	
<b>Chest Imaging</b> . . . . .	<b>4</b>	<b>Nuclear Medicine</b> . . . . .	<b>26</b>
Chest X-Ray (CXR)		Brain	
Computed Tomography (CT) Chest		Thyroid	
Lung Abnormalities		Respiratory	
Pulmonary Vascular Abnormalities		Cardiac	
Pleural Abnormalities		Abdomen and Genitourinary System	
Mediastinal Abnormalities		Bone	
Tubes, Lines, and Catheters			
<b>Abdominal Imaging</b> . . . . .	<b>10</b>	<b>Interventional Radiology</b> . . . . .	<b>28</b>
Abdominal X-Ray (AXR)		Vascular Procedures	
Approach to Abdominal X-Ray (AXR)		Nonvascular Interventions	
Approach to Abdominal Computed Tomography (CT)			
Contrast Studies		<b>Breast Imaging</b> . . . . .	<b>30</b>
Specific Visceral Organ Imaging		Modalities	
“itis” Imaging		Breast Interventional Procedures	
Angiography of GI Tract		Breast Findings	
<b>Genitourinary System and Adrenal</b> . . . . .	<b>16</b>	<b>References</b> . . . . .	<b>32</b>
Urological Imaging			
Gynecological Imaging			
Adrenal Mass			
<b>Neuroradiology</b> . . . . .	<b>18</b>		
Modalities			
Approach to CT Head			
Selected Pathology			

## Acronyms

AXR	abdominal x-ray	FLAIR	fluid-attenuated inversion recover	PBD	percutaneous biliary drainage
CT	computed tomography	HIDA	hepatobiliary iminodiacetic acid	PET	positron emission tomography scan
CTA	computed tomographic angiogram	HSG	hysterosalpingogram	PTA	percutaneous transluminal angioplasty
DEXA	dual-energy x-ray absorptiometry	IVP	intravenous pyelogram	RAIU	radioactive iodine uptake
DSA	digital subtraction angiography	MRA	magnetic resonance angiogram	SPECT	single photon emission computed tomography
DWI	diffusion-weighted image	MRCP	magnetic resonance cholangiopancreatography	TRUS	transrectal ultrasound
ERCP	endoscopic retrograde cholangio-pancreatography	MRI	magnetic resonance imaging	TVUS	transvaginal ultrasound
		MUGA	multiple gated acquisition scan	VCUG	voiding cystourethrogram

# Imaging Modalities

## X-Ray Imaging

- x-rays, or Roentgen rays, are a form of electromagnetic energy of short wavelength
- as x-ray photons traverse matter, they can be absorbed (a process known as “attenuation”) and/or scattered
- the density of a structure determines its ability to attenuate or “weaken” the x-ray beam
  - air < fat < water < bone < metal
- structures that have high attenuation, e.g. bone, appear white on the resulting images

## Plain Films

- x-rays pass through the patient and interact with a detection device to produce a 2-dimensional projection image
- structures closer to the film appear sharper and less magnified
- contraindications: pregnancy (relative)
- advantages: inexpensive, non-invasive, readily available
- disadvantages: radiation exposure, generally poor at distinguishing soft tissues

## Fluoroscopy

- continuous x-rays allow real-time visualization
- used for guiding angiographic and interventional procedures, in contrast examinations of the GI tract, and in the OR for certain surgical procedures (e.g. orthopedic, urological)
- on the fluoroscopic image black and white are reversed so that bone and contrast agents appear dark and radiolucent structures appear light

## Computed Tomography (CT)

- x-ray beam opposite a detector moves in a continuous 360 degree arc as patient is advanced through the imaging system
  - subsequent computer assisted reconstruction of anatomical structures from the axial plane
- attenuation is quantified in Hounsfield units:
  - adjusting the “window width” (range of Hounsfield units displayed) and “window level” (midpoint value of the window width) can maximally visualize certain anatomical structures
    - e.g. CT chest can be viewed using “lung”, “soft tissue” and “bone” settings
- contraindications: pregnancy (relative), contraindications to contrast agents (e.g. allergy, renal failure)
- advantages: delineates surrounding soft tissues, excellent at delineating bones and identifying lung/liver masses, may be used to guide biopsies, spiral CT has fast data acquisition, helical CT allows 3D reconstruction, CT angiography is less invasive than conventional angiography
- disadvantages: high radiation exposure, IV contrast injection, anxiety of patient when going through scanner, higher cost and less available than plain film

## Ultrasound (U/S)

- high frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
- reflection (or “echo”) occurs when the sound waves pass through tissue interfaces of different acoustic densities
- structures are described based on their echogenicity; hyperechoic structures appear bright whereas hypoechoic structures appear dark
- higher ultrasound frequencies result in greater resolution but greater attenuation (i.e. deeper structures more difficult to visualize)
- artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (i.e. tissue/air) or absorbs (tissue/bone) sound waves; enhancement refers to the increase in reflection amplitude (increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
- Doppler: determines the velocity of blood flowing past the transducer based on the Doppler effect
- Duplex scan: Doppler + visual images
- advantages: relatively low cost, non-invasive, no radiation, real time imaging, may be used for guided biopsies, many different imaging planes (axial, sagittal), determines cystic versus solid
- disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus



### Typical Effective Doses from Diagnostic Medical Exposures (in adults)\*

Diagnostic Procedure	Equivalent Number of Chest X-rays	Approximate Equivalent Period of Natural Background Radiation** (~3 mSv/yr)
<b>X-ray examinations:</b>		
Skull	5	12 d
Cervical spine	10	3 wk
Thoracic spine	50	4 mo
Lumbar spine	75	6 mo
Chest (single PA film)	1	2 d
Shoulder	0.5	1 d
Mammography	20	7 wk
Abdomen	35	3 mo
Hip	35	3 mo
Pelvis	30	10 wk
Knee	0.25	<1 d
IVU	150	1 yr
Dual-energy x-ray absorptiometry (without/with CT)	0.5/2	<1 d/4 d
Upper GI series	300	2 yr
Small bowel series	250	20 mo
Barium enema	400	2.7 yr
<b>CT procedures:</b>		
Head	100	8 mo
Neck	150	1 yr
Spine	300	2 yr
Chest	350	2.3 yr
Chest (pulmonary embolism)	750	5 yr
Coronary angiography	800	5.3 yr
Abdomen	400	2.7 yr
Pelvis	300	2 yr
<b>Radionuclide studies:</b>		
Brain ( <sup>18</sup> F)FDG	705	4.7 yr
Bone ( <sup>99m</sup> Tc)	315	2.1 yr
Thyroid ( <sup>99m</sup> Tc)	240	1.6 yr
Thyroid ( <sup>123</sup> I)	95	8 mo
Cardiac rest-stress test ( <sup>99m</sup> Tc 1-d)	470	3 yr
( <sup>99m</sup> Tc 2-d)	640	4 yr
Lung ventilation ( <sup>133</sup> Xe)	25	2 mo
Lung perfusion ( <sup>99m</sup> Tc)	100	8 mo
Renal ( <sup>99m</sup> Tc)	90-165	7-13 mo
Liver-spleen ( <sup>99m</sup> Tc)	105	8.4 yr
Biliary tract ( <sup>99m</sup> Tc)	155	1 yr

\*Source: *Radiology* 2008;248:254-263

\*\*Calculated using average natural background exposure in Canada (Health Canada: <http://www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/expos-eng.php>)



Substance	Hounsfield Unit
Air	-1000
Fat	-120
Water	0
Blood	+30 to +45
Muscle	+40
Contrast	+130
Bone	+400 or more



### Attenuation

Bone (= bright) > grey matter > white matter (“fatty” myelin) > CSF > air (= dark)

## Magnetic Resonance Imaging (MRI)

- non-invasive technique that does not use ionizing radiation
- able to produce images in virtually any plane
- patient is placed in a magnetic field; protons (H+) align themselves along the plane of magnetization due to intrinsic polarity. A pulsed radiofrequency beam is subsequently turned on which deflects all the protons off their aligned axes due to absorption of energy from the radiofrequency beam. When the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed. This energy is measured with a detector and interpreted by a computer to generate MR images.
- the MR image reflects the signal intensity picked up by the receiver. This signal intensity is dependent on:
  1. hydrogen density: tissues with low hydrogen density (e.g. cortical bone, lung) generate little to no MR signal compared to tissues with high hydrogen density (e.g. water)
  2. magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment (see Table 1)



Remember that water is “white” on T2 as “World War II”

**Table 1. Differences between Diffusion, T1- and T2-Weighted MR Imaging**

Imaging Techniques	Contrast Enhancements	Main Application	Advantages
Diffusion Weighted Imaging	Contrast dependent on the molecular motion of water. Decreased diffusion is hyperintense (bright), whereas increased diffusion is hypointense (dark)	Neuroradiology	Sensitive for detection of acute ischemic stroke and differentiating an acute stroke from other neurologic pathologies. An acute infarction will appear hyperintense
T1-Weighted	Fluid is hypointense (dark) and fat is hyperintense (bright)	Body soft tissues	Often considered an anatomic scan since they provide a reference for functional imaging
T2-Weighted	Fluid is hyperintense (bright) and fat is hypointense (dark)	Body soft tissues	Often considered a pathologic scan since they will highlight edematous areas associated with certain pathologies



**Recommended Premedication Protocol to Reduce the Frequency and/or Severity of Reactions to Contrast Media**

- Prednisone 50 mg PO at 13 h, 7 h, 1 h before contrast media injection plus diphenhydramine (Benadryl®) 50 mg IV, IM by 1 h before contrast medium

## Positron Emission Tomography Scans (PET)

- non-invasive technique that involves exposure to ionizing radiation (~7 mSv)
- nuclear medicine imaging technique that produces images of functional processes in the body
- current generation models integrate PET and CT technologies into a single imaging device (PET-CT) that collects both anatomic and functional information during a single acquisition
- positron-producing radioisotope, such as 18-fluorodeoxyglucose (18-FDG) is chemically incorporated into a metabolically active molecule (glucose), injected into patient, which travels to target organ, accumulates in tissues of interest, and as radioactive substance begins to decay, gamma rays are produced which are detected by PET scanner
- advantages: shows metabolism and physiology of tissues (not only anatomic), in oncology allows diagnosis, staging, restaging (lung, breast, colorectal, lymphoma, melanoma, esophageal, head and neck), has predictive and prognostic value (breast, lymphoma), can evaluate cardiac viability
- disadvantages: cost, ionizing radiation
- contraindications: pregnancy



**Contraindications to IV Contrast**

**MAD Failure**  
Multiple myeloma  
Adverse reaction previously  
Diabetes, Dehydration  
**Failure** (renal, severe heart)



**Acute Reactions to IV Contrast**

**Hot BUNS**  
Hypotension  
Bradycardia  
Urticaria  
Nausea/vomiting  
Seizures

## Contrast Enhancement

**Table 2. Contrast Agents**

Imaging Modality	Types	Advantages	Disadvantages	Contraindications
X-ray/CT	1. Barium (oral or rectal)	Radiopaque substance which helps to delineate intraluminal anatomy, may demonstrate patency, lumen integrity, or large filling defects	Risk of nephrotoxicity	Previous adverse reaction to contrast; barium enema is contraindicated in toxic megacolon, acute colitis, and suspected perforation
	2. Iodine (IV injection)	Delineates intraluminal anatomy, may demonstrate patency, lumen integrity, or large filling defects; under fluoroscopy, may also give information on function of an organ		Previous adverse reaction to contrast, renal failure, diabetes, pregnancy, multiple myeloma, severe heart failure and dehydration
MRI	1. Gadolinium-Chelates (IV injection)	Shortens T1 relaxation time, thereby increasing signal intensity in T1-weighted sequences; gadolinium has some effect on T2-relaxation time; highlights highly vascular structures (i.e. tumours)	Risk of nephrogenic systemic fibrosis in patients with end-stage renal disease	Previous adverse reaction to contrast or if end-stage renal disease (relative contraindication)
U/S	1. Microbubbles (IV injection)	Since gas is highly echogenic, the microbubbles allow for echo-enhancement of a tissue		Contraindicated in individuals with right-to-left cardiac shunts or people with known hypersensitivity reactions



# Chest Imaging

## Chest X-Ray (CXR)

### Standard Views

- posteroanterior (PA): anterior chest against film plate to minimize magnification of the heart size
- lateral: better visualization of retrocardiac space and thoracic spine (more sensitive at picking up pleural effusions)
  - helps localize lesions when combined with PA view
- anteroposterior (AP): for bedridden patients (generally a lower quality film than PA)
  - enlarged cardiac silhouette
- lateral decubitus: to assess for pleural effusion and pneumothorax in bedridden patients
- lordotic: angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs

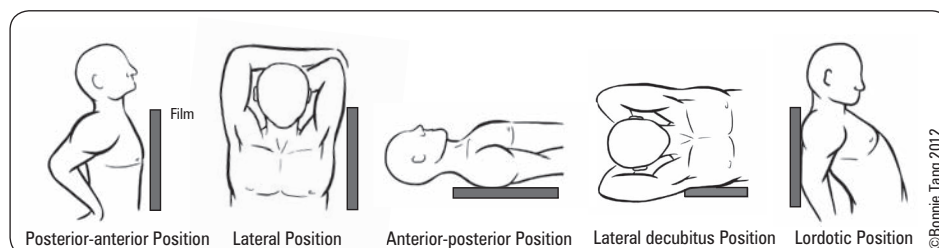


Figure 1. CXR views

### Approach to CXR

#### Basics

- ID: patient name, MRN, sex, age
- date of exam
- markers: Right and/or Left
- technique: view (e.g. PA, AP, lateral), supine or erect
- indications for the study
- comparison: date of previous study for comparison (if available)
- quality of film: inspiration (6th anterior and 10th posterior ribs should be visible), penetration (thoracic spine should be visible) and rotation (clavicles vs. spinous process)

#### Analysis

- tubes and lines: check position and be alert for pneumothorax or pneumomediastinum
- soft tissues: neck, axillae, pectoral muscles, breasts/nipples, chest wall
  - nipple markers can help identify nipples (may mimic lung nodules)
  - amount of soft tissue, presence of masses and air (subcutaneous emphysema)
- abdomen (see *Abdominal Imaging*, MI10):
  - free air under the diaphragm, air-fluid levels, distention in small and large bowels
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: C-spine, thoracic spine, shoulders, ribs, sternum, clavicles
  - lytic and blastic lesions and fractures
- mediastinum: trachea, heart, great vessels, mediastinum
  - cardiomegaly (cardiothoracic ratio >0.5), tracheal shift, tortuous aorta, widened mediastinum
- hila: pulmonary vessels, mainstem bronchi, and segmental bronchi, lymph nodes
- lungs: lung parenchyma, pleura, diaphragm
  - spine sign: on lateral films, vertebral bodies should appear progressively radiolucent as one moves down the thoracic vertebral column. If they appear more radioopaque, it is an indication of pathology (i.e. consolidation in overlying left lower lobe)
  - comment on abnormal lung opacity, pleural effusions or thickening
  - right hemidiaphragm usually higher than left due to liver
  - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm



#### Sodium Bicarbonate plus N-acetylcysteine

##### Prophylaxis: A Meta-analysis

*JACC Cardiovasc Interv* 2009;2:1116-1124

**Study:** A meta-analysis of 10 RCTs.

**Objective:** To compare N-acetylcysteine (NAC) + sodium bicarbonate ( $\text{NaHCO}_3$ ) to NAC + normal saline hydration in prevention of acute kidney injury (AKI) from IV contrast.

**Patients:** Those receiving IV contrast for various indications (PCI, angiography, catheterization)

**Results:** Combination treatment of NAC with intravenous  $\text{NaHCO}_3$  reduced contrast-induced AKI by 35% (relative risk: 0.65; 95% confidence interval: 0.40 to 1.05). However, the combination of N-acetylcysteine plus  $\text{NaHCO}_3$  did not significantly reduce renal failure requiring dialysis.

**Conclusion:** Combination prophylaxis should be considered for all high-risk patients (emergent cases or patients with chronic kidney disease).

Anatomy

Localizing Lesions

- silhouette sign: loss of normal interfaces due to lung pathology (consolidation, atelectasis, mass), which can be used to localize disease in specific lung segments (see Table 3)
  - note that pleural or mediastinal disease can also produce the silhouette sign

Table 3. Localization Using the Silhouette Sign

Interface Lost	Location of Lung Pathology
Superior vena cava/right superior mediastinum	RUL
Right heart border	RML
Right hemidiaphragm	RLL
Aortic knob/left superior mediastinum	LUL
Left heart border	Lingula
Left hemidiaphragm	LLL

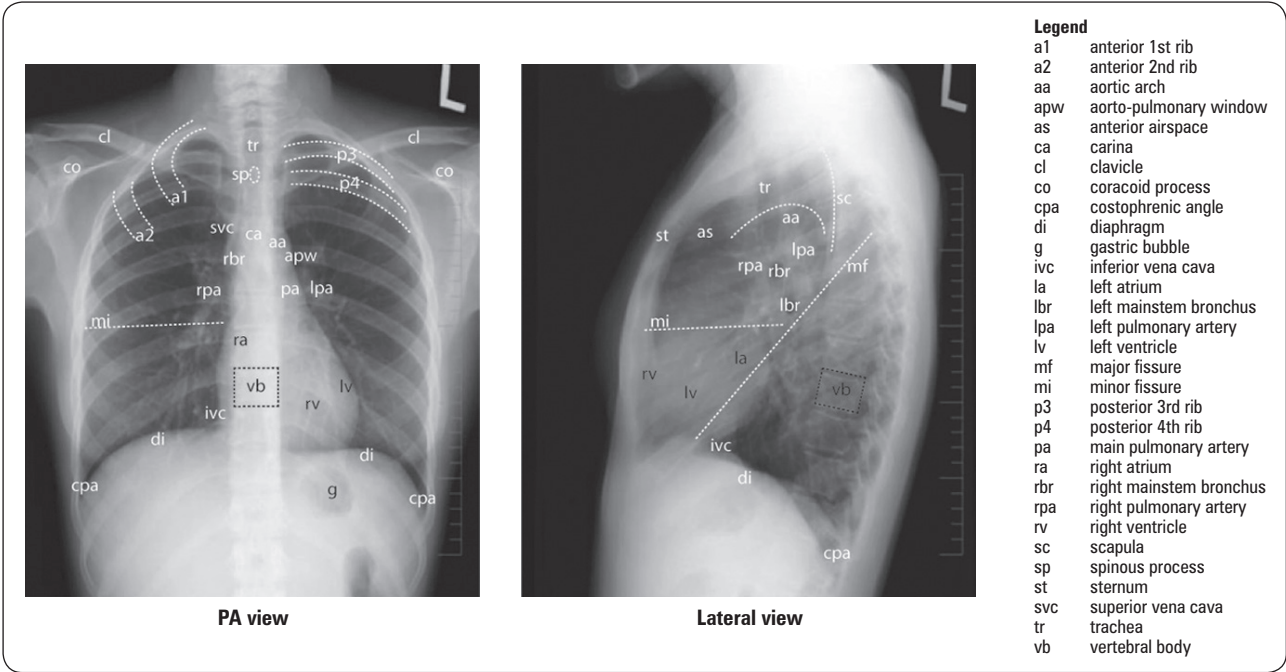


Figure 2. Location of fissures, mediastinal structures and bony landmarks

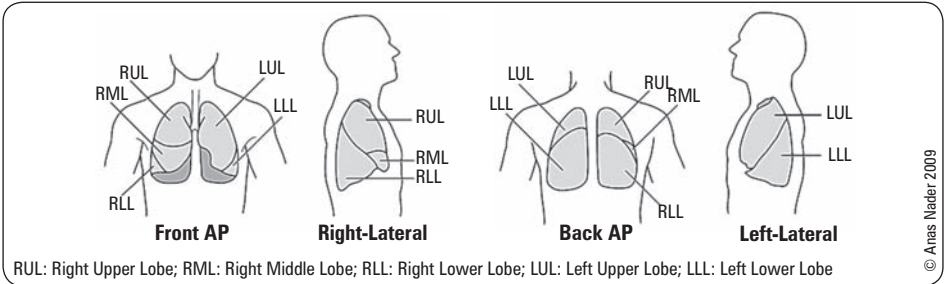


Figure 3. Location of lobes of the lung



Chest X-Ray Interpretation

Basics ABCDEF:

- AP, PA or other view
- Body position/rotation
- Confirm name
- Date
- Exposure/quality
- Films for comparison

Analysis ABCDEF:

- Airways, and hilar Adenopathy
- Bones and Breast shadows
- Cardiac silhouette and Costophrenic angle
- Diaphragm and Digestive tract
- Edges of pleura
- Fields (lung fields)

## Computed Tomography (CT) Chest

### Approach to CT Chest

- soft tissue window
  - thyroid, chest wall, pleura
  - heart: chambers, coronary artery calcifications, pericardium
  - vessels: aorta, pulmonary artery, smaller vasculature
  - lymph nodes: mediastinal, axillary
- bone window
  - look at vertebrae, sternum, manubrium, ribs for fractures, lytic lesions, sclerosis
- lung window
  - central-trachea: patency, secretions
  - bronchial trees: anatomic variants, mucus plugs, airway collapse
  - lung parenchyma: fissures, nodules, fibrosis/interstitial changes
  - pleural space: effusions

Table 4. Types of CT Chest

	Standard	High Resolution	Low Dose	CT Angiography
<b>Advantage</b>	Scans full lung very quickly (<1 min)	Thinner slices provide high definition of lung parenchyma	1/5th the radiation	Iodinated contrast highlights vasculature
<b>Disadvantage</b>	Poor at evaluating diffuse disease	Only 5-10% lung is sampled	Decreased detail	Contrast can cause severe allergic reaction and is nephrotoxic
<b>Contrast</b>	±	No	No	Yes
<b>Indication</b>	CXR abnormality Pleural and mediastinal abnormality Lung cancer staging Follow up metastases Empyema vs. abscess	Hemoptysis Diffuse lung disease (e.g. sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis) Pulmonary fibrosis Normal CXR but abnormal PFTs Characterize solitary pulmonary nodule	Screening Follow up infections, lung transplant, metastases	Pulmonary embolism Aortic aneurysms Aortic dissection

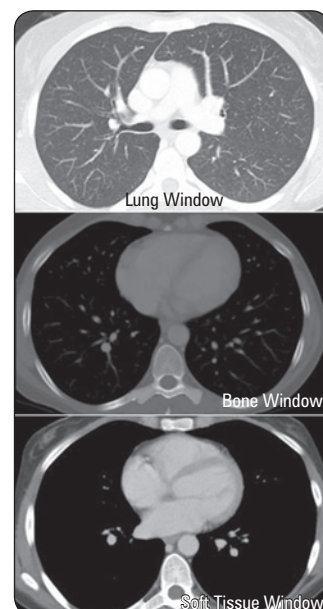


Figure 4. CT thorax windows



### DDx of Airspace Disease

- Pus (e.g. infections such as pneumonia, non-infectious inflammatory process)
- Fluid (e.g. pulmonary edema)
- Blood (e.g. pulmonary hemorrhage)
- Cells (e.g. bronchioalveolar carcinoma, lymphoma)
- Protein (e.g. alveolar proteinosis)

## Lung Abnormalities

### Atelectasis

- pathogenesis: collapse of alveoli due to restricted breathing, blockage of bronchi, external compression or poor surfactant
- findings:
  - increased opacity of involved segment/lobe, vascular crowding, silhouette sign, air bronchograms
  - volume loss: fissure deviation, hilar/mediastinal displacement, diaphragm elevation
  - compensatory hyperinflation of remaining normal lung
- differential diagnosis:
  - obstructive (most common): air distal to obstruction is reabsorbed causing alveolar collapse
    - ♦ endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury) or mucous plug (cystic fibrosis)
  - compressive:
    - ♦ tumour, bulla, effusion, enlarged heart, lymphadenopathy
  - traction (cicatization): due to scarring, which distorts alveoli and contracts the lung
  - adhesive: due to lack of surfactant
    - ♦ hyaline membrane disease, prematurity
  - passive (relaxation): a result of air or fluid in the pleural space
    - ♦ pleural effusion, pneumothorax
- management: in the absence of a known etiology, persisting atelectasis must be investigated (CT thorax) to rule out a bronchogenic carcinoma

### Consolidation

- pathogenesis: fluid (water, blood), inflammatory exudates, protein, or tumour in alveoli
- findings:
  - air bronchograms: lucent branching bronchi visible through opacification
  - airspace nodules: fluffy, patchy, poorly defined margins with later tendency to coalesce, may take on lobar or segmental distribution
  - silhouette sign

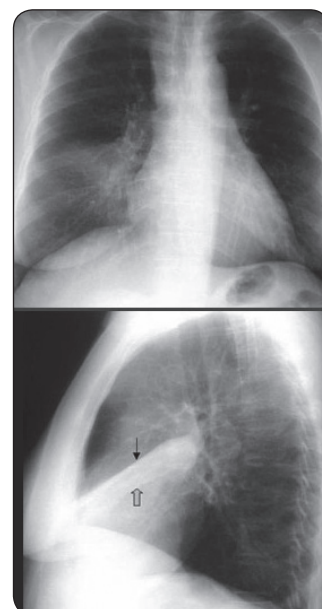


Figure 5. Atelectasis: RML collapse

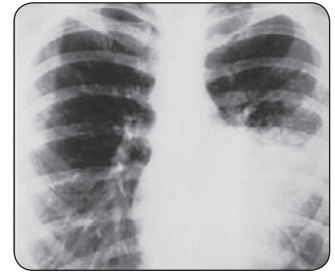
- differential diagnosis:
  - fluid: pulmonary edema, blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
  - inflammatory exudates: bacterial infections, TB, allergic hypersensitivity alveolitis, bronchiolitis obliterans organizing pneumonia (BOOP), allergic bronchopulmonary aspergillosis (ABPA), aspiration, sarcoidosis
  - protein: pulmonary alveolar proteinosis
  - tumour: bronchioalveolar carcinoma, lymphoma
- management: varies depending on the pattern of consolidation, which can suggest different etiologies. Management should also be done in the context of clinical picture

### Interstitial Disease

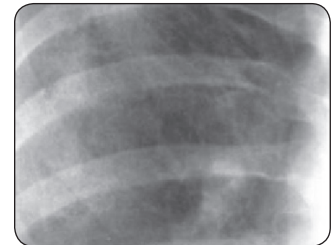
- pathogenesis: pathological process involving the interlobular connective tissue (i.e. “scaffolding of the lung”)
- findings:
  - linear: fine lines caused by thickened connective tissue septae
    - ♦ Kerley A: long thin lines in upper lobes
    - ♦ Kerley B: short horizontal lines extending from lateral lung margin
    - ♦ Kerley C: diffuse linear pattern throughout lung
    - ♦ seen in pulmonary edema, lymphangitic carcinomatosis and atypical interstitial pneumonias
  - nodular: 1-5 mm well-defined nodules distributed evenly throughout lung
    - ♦ seen in malignancy, pneumoconiosis and granulomatous disease (sarcoidosis, miliary TB)
  - reticular (honeycomb): parenchyma replaced by thin-walled cysts suggesting extensive destruction of pulmonary tissue and fibrosis (see Figures 7 and 8)
    - ♦ seen in interstitial pulmonary fibrosis (IPF), asbestosis and CVD
    - ♦ NOTE: watch for pneumothorax as a complication
  - reticulonodular: combination of reticular and nodular patterns
  - may also see signs of airspace disease (atelectasis and consolidation)
- differential diagnosis:
  - occupational/environmental exposure
    - ♦ inorganic: asbestosis, coal miner's pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
    - ♦ organic: hypersensitivity pneumonitis, bird fancier's lung, farmer's lung (moldy hay), and other organic dust
  - autoimmune: CVD (e.g. rheumatoid arthritis, scleroderma, SLE, polymyositis, mixed connective tissue disease), IBD, celiac disease, vasculitis
  - drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, phenytoin, carbamazepine, fluoxetine, amiodarone, chemotherapy (e.g. methotrexate), heroin, cocaine, methadone
  - infections: non-tuberculous mycobacteria, certain fungal infections
  - idiopathic: hypersensitivity pneumonitis, IPF, BOOP
  - for *Causes of Interstitial Lung Disease Classified by Distribution*, see [Respirology](#), R12
- management: high resolution CT thorax and biopsy

### Pulmonary Nodule (see Table 5)

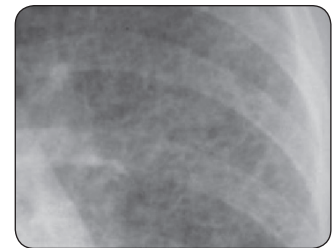
- findings: round opacity ± silhouette sign
  - note: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers
- differential diagnosis:
  - extrapulmonary density: nipple, skin lesion, electrode, pleural mass, bony lesion
  - solitary nodule:
    - ♦ tumour: carcinoma, hamartoma, metastasis, bronchial adenoma
    - ♦ inflammation: histoplasmosis, tuberculoma, coccidioidomycosis
    - ♦ vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
  - multiple nodules: metastases, abscess, granulomatous lung disease [TB, fungal, sarcoid, rheumatoid nodules, silicosis, granulomatosis with polyangiitis (GPA)]
- management: clinical information and CT appearance determine level of suspicion of malignancy
  - if high probability of malignancy, invasive testing (fine needle aspiration, transbronchial/transsthoracic biopsy) is indicated
  - if low probability of malignancy, repeat CXR or CT in 1-3 mo and then every 6 mo for 2 yr; if no change, then >99% chance benign



**Figure 6. Consolidation: bacterial pneumonia**



**Figure 7. Interstitial disease: fine reticular pattern**



**Figure 8. Interstitial disease: medium reticular pattern**



#### DDx of Interstitial Lung Disease

**FASSTEN** (upper lung disease)  
 Farmer's lung (hypersensitivity pneumonitis)  
 Ankylosing spondylitis  
 Sarcoidosis  
 Silicosis  
 TB  
 Eosinophilic granuloma (Langerhans cell histiocytosis)  
 Neurofibromatosis

**BAD RASH** (lower lung disease)  
 Bronchiolitis obliterans with organizing pneumonia (BOOP)  
 Asbestos  
 Drugs (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs)  
 Rheumatological disease  
 Aspiration  
 Scleroderma  
 Hamman Rich (interstitial pulmonary fibrosis) and idiopathic pulmonary fibrosis



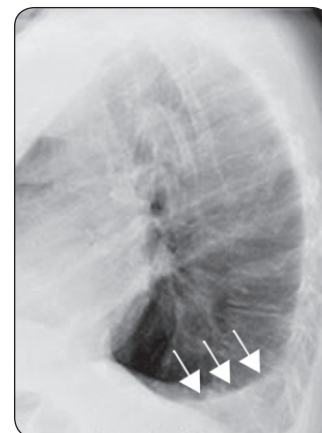
#### DDx for Cavitating Lung Nodule

**WEIRD HOLES**  
 GPA (Wegener's)  
 Embolic (pulmonary, septic)  
 Infection (anaerobes, pneumocystis, TB)  
 Rheumatoid (necrobiotic nodules)  
 Developmental cysts (sequestration)  
 Histiocytosis  
 Oncological  
 Lymphangioleiomyomatosis  
 Environmental, occupational  
 Sarcoidosis



**Table 5. Characteristics of Benign and Malignant Pulmonary Nodules**

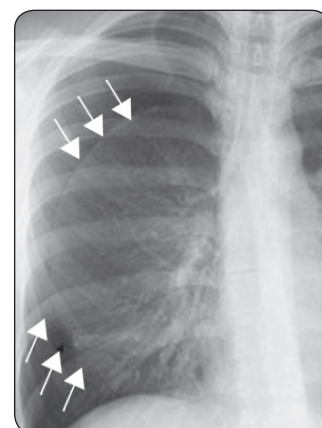
	Malignant	Benign
<b>Margin</b>	Ill-defined/spiculated ("corona radiata")	Well-defined
<b>Contour</b>	Lobulated	Smooth
<b>Calcification</b>	Eccentric or stippled	Diffuse, central, popcorn, concentric
<b>Doubling Time</b>	20-460 d	<20 d or >460 d
<b>Other Features</b>	Cavitation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history	
<b>Size</b>	>3 cm	<3 cm
<b>Cavitation</b>	Yes, especially with wall thickness >15 mm, eccentric cavity and shaggy internal margins	No
<b>Satellite Lesions</b>	No	Yes

**Figure 9. Pulmonary nodule: bronchogenic carcinoma****Figure 10. Pleural effusion in lateral view****Pulmonary Edema**

- pathogenesis: fluid accumulation in the airspaces of the lungs
- findings:
  - vascular redistribution/enlargement, cephalization, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
  - fluid initially collects in interstitium:
    - ♦ loss of definition of pulmonary vasculature
    - ♦ peribronchial cuffing
    - ♦ Kerley B lines
    - ♦ reticulonodular pattern
    - ♦ thickening of interlobar fissures
  - as pulmonary edema progresses, fluid begins to collect in alveoli causing diffuse air space disease often in a "bat wing" or "butterfly" pattern in perihilar regions with tendency to spare the outermost lung fields
- differential diagnosis: cardiogenic (CHF), renal failure, volume overload, non-cardiogenic (ARDS)

**Pulmonary Embolism**

- pathogenesis: arterial blockage in the lungs
- findings: Westermark sign (localized pulmonary oligemia), Hampton's hump (triangular peripheral infarct), enlarged RV and RA, atelectasis, pleural effusion, and rarely pulmonary edema
- management: V/Q scan, CT angiography (look for filling defect)

**Figure 11. Pneumothorax****Elevated Hemidiaphragm Suggests:**

**PAL DIP**  
 Pregnancy  
 Atelectasis  
 Lung resection  
 Diaphragmatic paralysis  
 Intra-abdominal process  
 Pneumectomy

Pleural effusion also may result in apparent elevation.

**Depressed Hemidiaphragm Suggests**

**TALC**  
 Tumour  
 Asthma  
 Large pleural effusion  
 COPD

**Pulmonary Vascular Abnormalities****Pleural Effusion****Table 6. Sensitivity of Plain Film Views for Pleural Effusion**

X-ray Projection	Minimum Volume to Visualize
Lateral decubitus	25 mL: most sensitive
Upright lateral	50 mL: meniscus seen in the posterior costophrenic sulcus
PA	200 mL
Supine	Diffuse haziness

- a horizontal fluid level is seen only in a hydropneumothorax (both fluid and air within pleural cavity)
- effusion may exert mass effect, shift trachea and mediastinum to opposite side, or cause atelectasis of adjacent lung
- U/S is superior to plain film for detection of small effusions and may also aid in thoracentesis

**Pneumothorax**

- pathogenesis: gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
- findings:
  - upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air
  - more obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiorly)
  - more difficult to detect on supine film; look for the "deep (costophrenic) sulcus" sign, "double diaphragm" sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  - mediastinal shift may occur if air is under tension (i.e. tension pneumothorax)

- differential diagnosis: spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, CVP line insertion), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung
- management: needle decompression or chest tube insertion, repeat CXR to ensure resolution

### Asbestos

- asbestos exposure may cause various pleural abnormalities including benign plaques (most common) that may calcify, diffuse pleural fibrosis, effusion, and malignant mesothelioma

## Mediastinal Abnormalities

### Mediastinal Mass

- the mediastinum is divided into three compartments; this provides the approach to the differential diagnosis of a mediastinal mass
- anterior (anterior border formed by anterior trachea and posterior border by the heart and great vessels)
  - 4 Ts: see sidebar
  - cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
- middle (extending behind anterior mediastinum to a line 1 cm posterior to the anterior border of the thoracic vertebral bodies)
  - esophageal carcinoma, esophageal duplication cyst
  - metastatic disease
  - lymphadenopathy (all causes)
  - hiatus hernia
  - bronchogenic cyst
- posterior (posterior to the middle line described above)
  - neurogenic tumour (e.g. neurofibroma, schwannoma)
  - multiple myeloma
  - pheochromocytoma
  - neurenteric cyst
  - thoracic duct cyst
  - lateral meningocele
  - Bochdalek hernia
  - extramedullary hematopoiesis
- in addition, any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, and hematoma



#### DDx Anterior Mediastinal Mass

##### 4 Ts

Thyroid  
Thymic neoplasm  
Teratoma  
Terrible lymphoma



#### DDx of Increased Cardiothoracic Ratio

- Cardiomegaly (myocardial dilatation or hypertrophy)
- Pericardial effusion
- Poor inspiratory effort/low lung volumes
- Pectus excavatum
- Antero-posterior view



#### Mediastinal Masses

Approximately 60% of anterior, 30% of middle, and 15% of posterior mediastinal masses are malignant.

### Enlarged Cardiac Silhouette

- heart borders
  - on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
  - on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle
- cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
  - using a good quality erect PA chest film in adults, cardiothoracic ratio of >0.5 is abnormal
  - differential of ratio >0.5
    - ♦ cardiomegaly (myocardial dilatation or hypertrophy)
    - ♦ pericardial effusion
    - ♦ poor inspiratory effort/low lung volumes
    - ♦ pectus excavatum
  - ratio <0.5 does not exclude enlargement (e.g. cardiomegaly + concomitant hyperinflation)
- pericardial effusion
  - globular heart with loss of indentations on left mediastinal border
- right atrial enlargement
  - increase in curvature of right heart border and enlargement of SVC
- left atrial enlargement
  - straightening of left heart border
  - increased opacity of lower right side of cardiovascular shadow (double heart border)
  - elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film), distance between left main bronchus and “double” heart border >7 cm, splayed carina (late sign)
- right ventricular enlargement
  - elevation of cardiac apex from diaphragm
  - anterior enlargement leading to loss of retrosternal air space on lateral
  - increased contact of RV against sternum
- left ventricular enlargement
  - displacement of cardiac apex inferiorly and posteriorly – “boot-shaped” heart

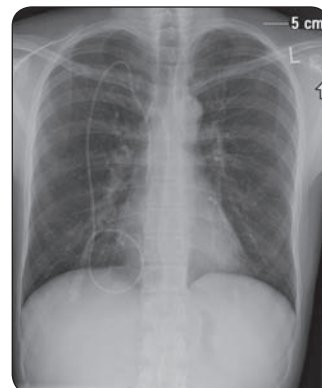


## Tubes, Lines, and Catheters

- ensure appropriate placement and assess potential complications of lines and tubes
- avoid mistaking a line/tube for pathology (e.g. oxygen rebreather mask for pneumothoraces)

### Central Venous Catheter

- used for fluid and medication administration, vascular access for hemodialysis, and central venous pressure (CVP) monitoring
- tip must be located distal to (above) right atrium to prevent inducing arrhythmias or perforating wall of atrium
  - if monitoring CVP, catheter tip must be proximal to venous valves
- tip of well positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle and inferiorly by top of RA
- course should parallel course of SVC – if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism



**Figure 12. Well positioned central venous catheter (CXR)**

### Endotracheal Tube

- frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- tip should be located 4 cm above tracheal carina – avoids bronchus intubation and vocal cord irritation
- maximum inflation diameter <3 cm to avoid necrosis of tracheal mucosa and rupture – ensure diameter of balloon is less than tracheal diameter above and below balloon
- complications: aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

### Nasogastric Tube (NG Tube)

- tip and sideport of NG tube should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- complications: aspiration (parenchymal opacities), intracranial perforation (trauma patients), pneumothorax

### Swan-Ganz Catheter

- to monitor pulmonary capillary wedge pressure and to measure cardiac output for suspected left ventricular dysfunction
- tip should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- if tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

### Chest Tube

- in dorsal and caudal portion of pleural space to evacuate fluid usually
- in ventral and cephalad portions of pleural space to evacuate pneumothoraces
- tube may lie in fissure as long as functioning
- complications: lung perforation (mediastinal opacities)

## Abdominal Imaging

### Abdominal X-Ray (AXR)

- indications:
  - acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction (SBO), large bowel obstruction (LBO)
  - chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
  - not useful in: GI bleeds, chronic anemia, vague GI symptoms
- AXR 3 most common views: left lateral decubitus (LLD), supine, erect upright



#### 3 Views of AXR

- Left lateral decubitus
- Supine
- Erect/Upright

## Anatomy

- abdomen divided into 2 cavities:
  - peritoneal cavity: lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
  - retroperitoneal cavity: contains several organs situated posterior to the peritoneal cavity; the contour of these can often be seen on radiographs

**Table 7. Differentiating Small and Large Bowel**

Property	Small Bowel	Large Bowel
Mucosal Folds	Uninterrupted valvulae conniventes (or plicae circularis)	Interrupted haustra extend only partway across lumen
Location	Central	Peripheral (picture frame)
Maximum diameter	3 cm	6 cm (9 cm at cecum)
Maximum fold thickness	3 mm	5 mm
Other	Rarely contains solid fecal material	Commonly contains solid fecal material



### What's in the Retroperitoneum?

- Duodenum (2nd, 3rd, 4th part)
- Ascending and descending colon
- Rectum
- Kidneys, ureters, bladder, adrenals
- Psoas, quadratus lumborum
- Aorta, inferior vena cava

## Approach to Abdominal X-Ray (AXR)

- mnemonic: "Free ABDO"
- Free = free fluid
  - small amounts of fluid: increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
  - large amounts of fluid: diffuse increased opacification on supine film; bowel floats to centre of anterior abdominal wall
  - ascites and blood (hemoperitoneum) are the same density on the radiograph and therefore cannot be differentiated
- A = air
  - volvulus – twisting of the bowel upon itself; from most to least common:
    - ♦ sigmoid: "coffee bean" sign (massively dilated sigmoid projects to right or mid-upper abdomen) with proximal large bowel dilation
    - ♦ cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
    - ♦ gastric: rare
    - ♦ small bowel: "corkscrew sign" (rarely diagnosed on plain films, seen best on CT)
  - toxic megacolon
    - ♦ manifestation of fulminant colitis
    - ♦ extreme dilatation of colon (>6.5 cm) with mucosal changes including foci of edema, ulceration and pseudopolyps, loss of normal haustral pattern
- B = bowel wall thickening
  - increased soft tissue density in bowel wall, thumb-like indentations in bowel wall ("thumb-printing"), or a picket-fence appearance of the valvulae conniventes ("stacked coin" appearance)
  - may be seen in IBD, infection, ischemia, hypoproteinemic states, and submucosal hemorrhage
- D = densities
  - bones: look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
  - abnormal calcifications: approach by location
    - ♦ RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
    - ♦ RLQ: ureteral stone, appendicolith, gallstone ileus
    - ♦ LUQ: renal stone, adrenal calcification, tail of pancreas
    - ♦ LLQ: ureteral stone
    - ♦ central: aorta/aortic aneurysm, pancreas, lymph nodes
    - ♦ pelvis: phleboliths (calcified veins), uterine fibroids, bladder stones
- O = organs
  - kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
  - outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)



### Approach to AXR

#### Free ABDO

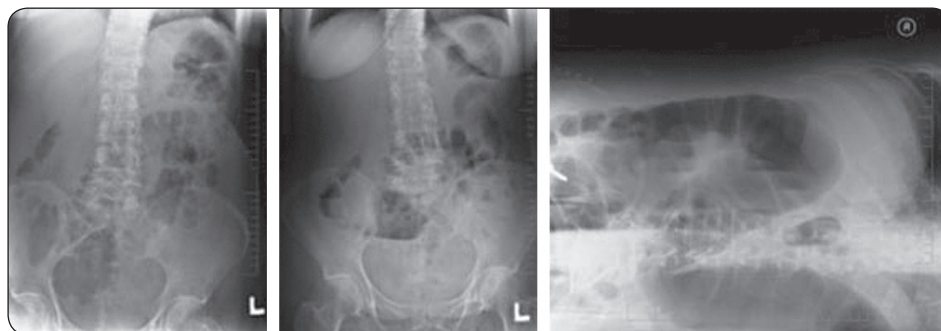
Free fluid

Air

Bowel wall thickening

Densities (bones, calcifications)

Organs



**Figure 13. Normal AXRs: (left) supine anteroposterior AXR, (middle) upright anteroposterior AXR, and (right) left lateral decubitus AXR**

**Table 8. Abnormal Air on Abdominal X-Ray**

Air	Appearance	Common Etiologies
<b>Extraluminal</b>		
Intraperitoneal (pneumoperitoneum)	Upright film: air under diaphragm LLD film: air between liver and abdominal wall Supine film: gas outlines of structures not normally seen: • Inner and outer bowel wall (Rigler's sign) • Falciform ligament • Peritoneal cavity ("football" sign)	Perforated viscus Postoperative (up to 10 d to be resorbed)
Retroperitoneal	Gas outlining retroperitoneal structures allowing increased visualization: • Psoas shadows • Renal shadows	Perforation of retroperitoneal segments of bowel: duodenal ulcer, post-colonoscopy
<b>Intramural</b> (pneumatosis intestinalis)	Lucent air streaks in bowel wall, 2 types: 1. Linear 2. Rounded (cystoides type)	1. Linear: ischemia, necrotizing enterocolitis 2. Rounded/cystoides (generally benign): primary (idiopathic), secondary to COPD
<b>Intraluminal</b>	Dilated loops of bowel, air-fluid levels	Adynamic (paralytic) ileus, mechanical bowel obstruction (see Table 9)
<b>Loculated</b>	Mottled, localized in abnormal position without normal bowel features	Abscess (evaluate with CT)
<b>Biliary</b>	Air centrally over liver	Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis
<b>Portal Venous</b>	Air peripherally over liver in branching pattern	Bowel ischemia/infarction



#### Biliary vs. Portal Venous Air

"Go with the flow": air follows the flow of bile or portal venous blood. Biliary air is most prominent centrally over the liver. Portal venous air is most prominent peripherally.

**Table 9. Adynamic Ileus vs. Mechanical Obstruction**

Feature	Adynamic Ileus	Mechanical Obstruction
<b>Calibre of Bowel Loops</b>	Normal or dilated	Usually dilated
<b>Air-Fluid Levels</b> (erect and LLD films only)	Same level in the same single loop	Multiple air fluid levels giving "step ladder" appearance, dynamic (indicating peristalsis present), "string of pearls" (row of small gas accumulations in the dilated valvulae conniventes)
<b>Distribution of Bowel Gas</b>	Air throughout GI tract is generalized or localized • In a localized ileus (e.g. pancreatitis, appendicitis): dilated "sentinel loop" remains in the same location on serial films, usually adjacent to the area of inflammation	Dilated bowel up to the point of obstruction (i.e. transition point) No air distal to obstructed segment "Hairpin" (180°) turns in bowel



#### Ileocecal Valve (ICV) Function in Large Bowel Obstruction

##### Competent ICV

Distention of large bowel between obstruction and ICV; small bowel unaffected. Higher risk of perforation, especially with cecal distention > 10 cm.

##### Incompetent ICV

Distention of large and small bowel.

## Abdominal CT

- indications for plain CT: renal colic, hemorrhage
- indications for CT with contrast:
  - IV contrast given immediately before or during CT to allow identification of arteries and veins
    - ♦ portal venous phase: indicated for majority of cases
    - ♦ biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumours
  - oral contrast: barium or water soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
  - rectal contrast: given for investigation of colonic lesions
  - caution: contrast allergy (may premedicate with steroids and antihistamine)
  - contraindication: impaired renal function, based on eGFR

## Approach to Abdominal Computed Tomography (CT)

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ/structure individually, from top to bottom evaluating size and shape of each area of increased or decreased density
- evaluate the following
  - soft tissue window
    - ♦ liver, gallbladder, spleen and pancreas
    - ♦ adrenals, kidneys, ureters and bladder
    - ♦ stomach, duodenum, small bowel mesentery and colon/appendix
    - ♦ retroperitoneum: aorta, vena cava and mesenteric vessels; look for adenopathy in vicinity of vessels
    - ♦ peritoneal cavity for fluid or masses
    - ♦ abdominal wall and adjacent soft tissue
  - lung window
    - ♦ visible lung (bases)
  - bone window
    - ♦ vertebrae, spinal cord, and bony pelvis

### CT and Bowel Obstruction

- cause of bowel obstruction rarely found on plain films – CT is best choice for imaging
- the “3,6,9” rule is a very useful guide to determining when the bowel is dilated. The maximum diameter of the bowel is 3 cm for small bowel, 6 cm for large bowel and 9 cm for cecum. This can also be useful in distinguishing between small and large bowel and when assessing for ‘impending’ cecal perforation (post-untreated Ogilvie’s syndrome)

### CT Colonography (virtual colonoscopy)

- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumours)
- two CT scans of the abdomen (prone and supine) after the instillation of carbon dioxide into a prepped colon
- computer reconstruction of 2D CT images into a 3D intraluminal view of the colon in order to look for masses
- lesions seen on 3D images correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, staging of obstructing colonic lesions



#### Colorectal Cancer: CT Colonography and Colonoscopy for Detection- Systematic Review and Meta-Analysis

*Radiology* 2011;259:393-405

**Study:** Systematic review and meta-analysis.

**Population:** 49 studies on 11,151 patients undergoing diagnostic study for detection of colorectal cancer (CRC).

**Intervention:** CT colonography (CTC) and optical colonoscopy (OC).

**Main outcome measure:** Sensitivity of CTC and OC for CRC.

**Results:** CTC has a sensitivity of 96.1% (CI: 93.8%, 97.7%) and OC has a sensitivity of 94.7% (CI: 90.4%, 97.2%) for the detection of CRC.

**Authors' Conclusion:** CTC is highly sensitive for the detection of CRC and may be a better modality for the initial investigation of suspected CRC, assuming reasonable specificity.



Figure 14. Barium enema

## Contrast Studies

Table 10. Types of Contrast Studies

Study	Description	Indications	Assessment	Findings
<b>Cine Esophagogram</b>	Contrast agent swallowed Recorded for later playback and analysis	Dysphagia, swallowing incoordination, recurrent aspiration, post-op cleft palate repair	Cervical esophagus	Aspiration, webs (partial occlusion), Zenker's diverticulum, cricopharyngeal bar, laryngeal tumour
<b>Barium Swallow</b>	Contrast agent swallowed under fluoroscopy, selective images captured	Dysphagia, r/o GERD, post esophageal surgery	Thoracic esophagus	Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear
<b>Upper GI Series</b>	Double contrast study: 1. Barium to coat mucosa, then 2. Gas pills for distention Patient NPO after midnight	Dyspepsia, investigate possible UGI bleed, weight loss/anemia, post gastric surgery	Thoracic esophagus, stomach, or duodenum	Ulcers, neoplasms, filling defects
<b>Barium Enema</b>	Colon filled retrograde with barium and air or CO <sub>2</sub> Bowel prep the night before procedure	Altered bowel habits, suspected LGI bleed, weight loss/anemia, r/o large bowel obstruction, suspected perforation, check surgical anastomosis, history of polyps	Large bowel Rectum may be obscured by tube – therefore must do sigmoidoscopy to exclude rectal lesions	Diverticulosis, neoplasms, IBD, intussusception (can be reduced with barium or air enema), volvulus
<b>Small Bowel Follow Through</b>	Single contrast images following UGI series	GI bleed with nondiagnostic upper GI series/barium enema, weight loss/anemia, diarrhea, IBD, malabsorption, abdominal pain, post small bowel surgery	Entire small bowel	Neoplasms, IBD, malabsorption, infection
<b>Small Bowel Enema (enteroclysis)</b>	Duodenal intubation: 1. Barium/methyl cellulose infusion and fluoroscopic evaluation 2. CT enteroclysis with water infusion	IBD, malabsorption, weight loss/anemia, Meckel's diverticulum	Entire small bowel	Neoplasms, IBD, malabsorption, infection

## Specific Visceral Organ Imaging

### Liver

- U/S: assessment of cysts, abscesses, tumours, biliary tree
- CT ± IV: most popular procedure for imaging the liver parenchyma (primary liver tumours, metastases, cysts, abscesses, trauma, cirrhosis)
- MR: also excellent in evaluation of primary liver tumours, liver metastases, and other parenchymal conditions. It is particularly helpful in differentiating common benign hepatic hemangiomas from primary liver tumours and metastases
- findings:
  - altered liver size, contour, density
  - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
  - portal hypertension: increased portal vein diameter, collateral veins, splenomegaly ( $\geq 12$  cm), portal vein thrombosis, recanalization of the umbilical vein
  - varices (caput medusa, esophageal varices, porto-systemic shunts, dilated splenic vein)
  - splenomegaly and ascites
  - U/S: cirrhosis appears nodular and hyperechoic with irregular areas of atrophy of the right lobe and hypertrophy of the caudate or left lobes
  - CT: fatty infiltration appears hypodense
- investigation of liver masses
  - require contrast to visualize certain hepatic masses

**Table 11. Phases of Enhancement Following IV Contrast Bolus**

Phase	Time Frame	Uses
Arterial Phase	20-30 s	<ul style="list-style-type: none"> <li>• Early and late arterial phase possible on multidetector CT</li> <li>• Late arterial phase best for discriminating hypervascular HCC</li> </ul>
Portal Venous Phase	60-70 s	<ul style="list-style-type: none"> <li>• Provides maximum enhancement of hepatic tissue</li> <li>• Most tumours supplied by hepatic artery are relatively hypovascular, therefore appear as low-attenuation masses in portal venous phase</li> </ul>
Equilibrium Phase	120-180 s	<ul style="list-style-type: none"> <li>• Hypervascular tumours wash out (HCC)</li> <li>• Persistent enhancement suggests blood pool (hemangioma) or fibrous/scar tissue (HCC capsule, focal nodular hyperplasia, cholangiocarcinoma)</li> </ul>

**Table 12. Imaging of Liver Masses**

Mass	U/S	CT
Metastases	Multiple masses of variable echotexture	Usually low attenuation on contrast enhanced scan
HCC	Single/multiple masses, or diffuse infiltration	Hypervascular enhances in arterial and washes out venous phase with portal venous tumour thrombus
Abscess	Poorly defined, irregular margin, hypoechoic contents	Low-attenuation lesion with an irregular enhancing wall
Hydatid Cyst	Simple/multiloculated cyst	Low-attenuation simple or multiloculated cyst; calcification
Hemangioma	Homogenous hyperechoic mass	Peripheral globular enhancement in arterial phase scans; central-filling and persistent enhancement on delayed scans
Focal Nodular Hyperplasia	Well-defined mass, central scar seen in 50%	Hypervascular mass in arterial phase and iso-attenuation to liver in portal venous phase
Hepatic Adenoma	Most common in young women taking oral contraceptives. Well-defined mass with hyperechoic areas due to hemorrhage	Well-defined hypervascular lesion with enlarged central vessel becoming slightly isoattenuating in venous phase

### Spleen

- U/S, CT, and/or nuclear medicine scan
- CT for splenic trauma (hemorrhage)

### Biliary Tree

- U/S
  - bile ducts usually visualized only if dilated, secondary to obstruction (e.g. choledocholithiasis, benign stricture, mass)
- CT
  - dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- ERCP, MRCP, PTC: further evaluation of obstruction and possible intervention



Normal liver appears more dense than spleen on CT. If less dense, suspect fatty infiltration.



#### Liver Mass DDx

5 Hs  
HCC  
Hydatid cyst  
Hemangioma  
Hepatic adenoma  
Hyperplasia (focal nodular)



#### Revised Estimates of Diagnostic Test Sensitivity and Specificity in Suspected Biliary Tract Disease

*Arch Intern Med* 1998;154:2573-2581

**Purpose:** To assess the sensitivity and specificity of tests used to diagnose cholelithiasis and acute cholecystitis, including ultrasonography, oral cholecystography, radionuclide scanning with Technetium, MRI, CT.

**Study Characteristics:** Meta-analysis of 30 studies evaluating the use of different imaging modalities in the diagnosis of biliary tract disease.

**Participants:** No limits.

**Main Outcomes:** Sensitivity and specificity of the different imaging modalities, using the gold standard of surgery, autopsy, or 3 mo clinical follow-up for cholelithiasis. For acute cholecystitis, pathologic findings, confirmation of an alternate disease, or clinical resolution during hospitalization for cholecystitis were used as the standard.

**Results:** For evaluating cholelithiasis, U/S had the best unadjusted sensitivity (0.97; 95% CI, 0.95 to 0.99) and specificity (0.95, 95% CI, 0.88 to 1.00) and adjusted (for verification bias) sensitivity (0.84; 95% CI, 0.76 to 0.92) and specificity (0.99; 95% CI, 0.97 to 1.00). For evaluating acute cholecystitis, radionuclide scanning has the best sensitivity (0.97; 95% CI, 0.96 to 0.98) and specificity (0.90; 95% CI, 0.86 to 0.95).

**Conclusions:** U/S is the test of choice for diagnosing cholelithiasis and radionuclide scanning is the superior test for diagnosing acute cholecystitis.



**Figure 15. ERCP: biliary tree**



## Pancreas

- tumours
  - U/S: mass is more echogenic than normal pancreatic tissue
  - CT: preferred modality for diagnosis/staging
- ductal dilation secondary to stone/tumour
  - MRCP: imaging of ductal system using MRI cholangiography
  - ERCP: endoscope to inject dye into the biliary tree and X-ray imaging to assess pancreatic and biliary ducts; therapeutic potential (stent placement, stone retrieval); acute pancreatitis is a complication in 5% of diagnostic procedures and 10% of therapeutic procedures
- pancreatitis and/or its complications: pseudocyst, abscess, necrosis, splenic artery aneurysm (see "itis" Imaging below)

## "itis" Imaging

### Acute Cholecystitis

- pathogenesis: inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or, in the case of acalculous cholecystitis, due to gallbladder ischemia or cholestasis (see [General Surgery](#), GS46)
- best imaging modality: U/S (best sensitivity and specificity), nuclear medicine (HIDA scan) can help diagnose cases of acalculous or chronic cholecystitis
- findings: thick wall, pericholecystic fluid, gallstones, dilated gallbladder, positive sonographic Murphy's sign
- management: cholecystectomy

### Acute Appendicitis

- pathogenesis: luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess or peritonitis (see [General Surgery](#), GS28)
- best imaging modality: U/S or CT
- findings:
  - U/S: thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible
  - U/S may also demonstrate other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
  - CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage
- management: appendectomy

### Acute Diverticulitis

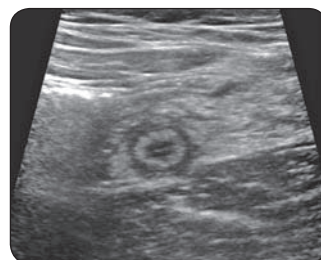
- pathogenesis: erosion of the intestinal wall (most commonly rectosigmoid) by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation (see [General Surgery](#), GS31)
- best imaging modality: CT is modality of choice, although U/S is sometimes used
- contrast: oral and rectal contrast given before CT to opacify bowel
- findings:
  - cardinal signs: thickened wall, mesenteric infiltration, gas-filled diverticula, abscess
  - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
  - sometimes difficult to distinguish from perforated cancer (therefore send abscess fluid for cytology and follow up with colonoscopy)
  - if chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)
- management: ranges from antibiotic treatment to surgical intervention. Can use imaging to follow progression

### Acute Pancreatitis

- pathogenesis: activation of proteolytic enzymes within pancreatic cells leading to local and systemic inflammatory response (see [Gastroenterology](#), G44). Clinical/biochemical diagnosis
- best imaging modality imaging used to support diagnosis and evaluate for complications (diagnosis cannot be excluded by imaging alone)
  - U/S good for screening and follow-up
  - CT is useful in advanced stages and in assessing for complications (1st line imaging test)
- findings:
  - U/S: hypoechoic enlarged pancreas (however if ileus present, gas obscures pancreas)
  - CT: enlarged pancreas, edema, stranding changes in surrounding fat with indistinct fat planes, mesenteric and Gerota's fascia thickening, pseudocyst in lesser sac, abscess (gas or thick-walled fluid collection), pancreatic necrosis (low attenuation gas-containing non-enhancing pancreatic tissue), hemorrhage
  - CT-guided needle aspiration and/or drainage done for abscess when clinically indicated
  - pseudocyst may be followed by CT and drained if symptomatic
- management: supportive therapy



**Figure 16. Ultrasound: inflamed gallbladder**



**Figure 17. Ultrasound: inflamed appendix**



#### Computed Tomography and Ultrasonography to Detect Acute Appendicitis in Adults and Adolescents

*Ann Intern Med* 2004;141:537-546

**Purpose:** To review the diagnostic accuracy of CT and ultrasonography in the diagnosis of acute appendicitis.

**Study Characteristics:** Meta-analysis of 22 prospective studies evaluating the use of CT or ultrasonography, followed by surgical or clinical follow-up in patients with suspected appendicitis.

**Participants:** Age 14 and older with a clinical suspicion of appendicitis.

**Main Outcomes:** Sensitivity and specificity using surgery or clinical follow-up as the gold standard. Results: CT (12 studies) had an overall sensitivity of 0.94 (95% CI, 0.91 to 0.95) and a specificity of 0.95 (95% CI, 0.93 to 0.96). Ultrasonography (14 studies) had an overall sensitivity of 0.86 (95% CI, 0.83 to 0.88) and a specificity of 0.81 (95% CI, 0.78 to 0.84).

**Conclusions:** CT is more accurate for diagnosing appendicitis in adults and adolescents, although verification bias and inappropriate blinding of reference standards were noted in the included studies.



Angiography requires active blood loss 1-1.5 mL/min under optimal conditions for a bleeding site to be visualized in cases of lower GI bleeding.



### Chronic Pancreatitis

- pathogenesis: (see [Gastroenterology](#), G46)
- best imaging modality: MRCP
- findings: U/S, CT scan and MRI may show calcifications, ductal dilatation, enlargement of the pancreas and fluid collections (e.g. pseudocysts) adjacent to the gland. However, magnetic resonance cholangiopancreatography (MRCP) is becoming the diagnostic test of choice since it can show calcification and pancreatic duct obstruction

## Angiography of GI Tract

- anatomy of the GI tract arterial blood supply branches
  - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
  - superior mesenteric artery (SMA): jejunal, ileal, ileo-colic, right colic, middle colic
  - inferior mesenteric artery (IMA): left colic, superior rectal
- imaging modalities
  - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
    - ♦ flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
  - CT angiogram: non-invasive using IV contrast (no catheterization required)

## Genitourinary System and Adrenal

### Urological Imaging

#### KUB (kidneys, ureters, bladder)

- a frontal supine radiograph of the abdomen
- **indication:** useful in evaluation of radio-opaque renal stones (all stones but uric acid and indinavir), as well as indwelling ureteric stents or catheters
- **findings:** addition of intravenous contrast excreted by the kidney (intravenous urogram) allows greater visualization of the urinary tract, but has been largely replaced by CT urography

#### Abdominal CT

##### Renal Masses

- Boznik classification for cystic renal masses
- classes I-II are benign and can be disregarded
- class IIF should be followed
- classes III-IV are suspicious for malignancy, requiring additional workup

**Table 13. Boznik Classification for Cystic Renal Masses**

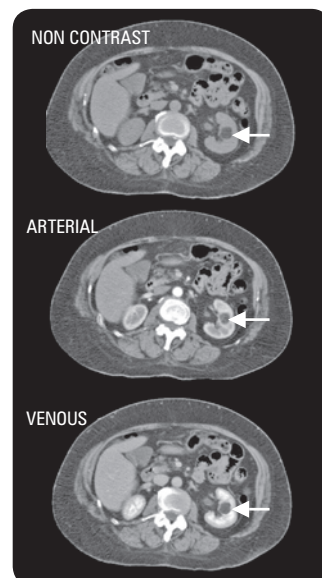
Classes	Definition
<b>Simple renal cysts</b>	
Class I	Fluid-attenuating well-defined lesion, no septation, no calcification, no solid components, hair thin wall
Class II	Same as class I + fine calcification or moderately thickened calcification in septae or walls; also includes hyperdense cysts (<3 cm) that do not enhance with contrast
<b>Complex renal cysts</b>	
Class III	Thick irregular walls, ± calcifications, ± septated, enhancing walls or septa with contrast
<b>Renal cell carcinoma</b>	
Class IV	Same as class III + soft tissue enhancement with contrast (defined as >10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase ± areas of necrosis

- **plain CT**
  - indications: general imaging of renal anatomy, although specific study types have supplanted plain CT for many indications, including CT urography (upper tract uroepithelial malignancies and renal calculi) and triphasic CT (renal masses)
- **CT urography**
  - indications: excretory phase imaging allows detailed assessment of urinary tracts, high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts, useful for assessment of renal calculi
- **triphase CT**
  - indications: standard imaging for renal masses, allows accurate assessment of renal arteries and veins and better characterization of suspicious renal masses, with particular utility in differentiating renal cell carcinoma from more benign masses
  - phases: unenhanced, nephrographic, and excretory

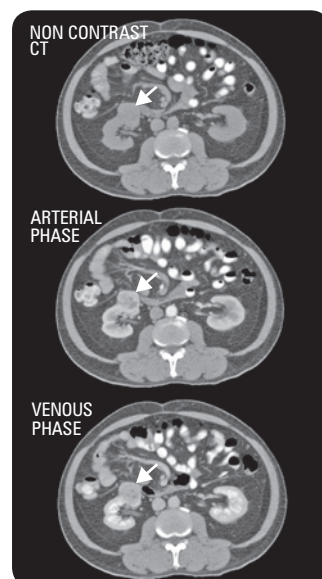


#### Imaging Modality Based on Presentation

- Acute testicular pain = Doppler, U/S
- Amenorrhea = U/S, MRI (brain)
- Bloating = U/S, CT
- Flank pain = U/S, CT
- Hematuria = U/S, Cystoscopy, CT
- Infertility = Hysterosalpingogram, MRI
- Lower abdominal mass = U/S, CT
- Lower abdominal pain = U/S, CT
- Renal colic = U/S, KUB, CT
- Testicular mass = U/S
- Urethral stricture = Urethrogram



**Figure 18. Triphasic CT of an angiomyolipoma:** showing fat density with non-contrast scan, mildly enhancing with contrast



**Figure 19. Triphasic CT of a renal cell carcinoma:** showing arterial enhancing right renal lesion with venous washout (shunting)

## U/S

- indications: initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic renal masses vs. complicated cysts); technique of choice for screening patients with suspected hydronephrosis (no intravenous contrast injection, no radiation to patient, and can be used in patients with renal failure); transrectal U/S (TRUS) useful to evaluate prostate gland and guide biopsies; doppler U/S to assess renal vasculature
- findings: solid renal masses are echogenic (bright on U/S), cystic renal masses have smooth well-defined walls with anechoic interior (dark on U/S), and complicated cysts have internal echoes within a thickened, irregular-wall

## Retrograde Pyelography

- indications: visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium, ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction)
- findings: only yields information about the collecting systems (renal pelvis and associated structures)
  - no information regarding the parenchyma of the kidney

## Voiding Cystourethrogram (VCUG)

- bladder filled with contrast to the point where voiding is triggered
- fluoroscopy (continuous, real-time) to visualize bladder
- indications: children with recurrent UTIs, hydronephrosis, hydroureter, suspected lower urinary tract obstruction or vesicoureteral reflux
- findings: contractility and evidence of vesicoureteric reflux

## Retrograde Urethrogram

- a small Foley catheter placed into penile urethral opening
- indications: used mainly to study strictures or trauma to the male urethra (Figure 20)

## MRI

- advantages: high spatial and tissue resolution, lack of exposure to ionizing radiation and nephrotoxic contrast agents
- indications: indicated over CT for depiction of renal masses in patients with previous nephron sparing surgery, patients requiring serial follow-ups (less radiation dosage), patients with reduced renal function, and patients with solitary kidneys

## Renal Nuclear Scan

Table 14. Renal Scan Tests

Type of Test	Uses	Radionuclide
<b>Renogram</b>	To assess renal function and collecting system: evaluation of renal failure, workup of urinary tract obstruction and hypertension, investigation of renal transplant	IV $^{99m}\text{Tc}$ -pentetate (DTPA) or mertiatide (MAG3), and imaged at 1-3 s intervals with a gamma camera over the first 60 s to assess perfusion
<b>Morphological</b>	Assess renal anatomy: investigation of pyelonephritis and cortical scars	$^{99m}\text{Tc}$ -DMSA $^{99m}\text{Tc}$ -glucoheptonate



Figure 20. Retrograde urethrogram: demonstrating stricture in the membranous urethra



Figure 21. Transabdominal ultrasound: pregnancy, 18 wk fetus

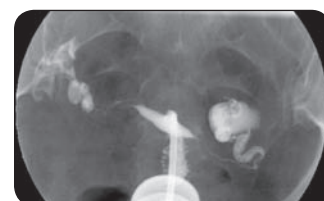


Figure 22. Hysterosalpingogram: left hydrosalpinx



Pregnancy should always be ruled out by  $\beta$ -HCG before CT of a female pelvis (or any organ system) is performed.

## Gynecological Imaging

### U/S

- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air containing loops of bowel
  - indication: good initial investigation for suspected pelvic pathology
- transvaginal approach provides enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves at reduced distances
  - indication: improved assessment of ovaries, first trimester development, and ectopic pregnancies

### Hysterosalpingogram

- indications: useful for assessing pathology of the uterine cavity and fallopian tubes, evaluating uterine abnormalities (e.g. bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)
- performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent

### CT/MRI

- indications: evaluating pelvic structures, especially those adjacent to the adnexa and uterus
- invaluable for staging gynecological malignancies

## Sonohysterogram

- saline infusion sonohysterogram involves instilling fluid into the uterine cavity transcervically to provide enhanced endometrial visualization during transvaginal ultrasound examination.
- indications: abnormal uterine bleeding, uterine cavity abnormalities that are suspected or noted on transvaginal sonography (i.e. leiomyomas, polyps, synechiae), congenital abnormalities of the uterine cavity, infertility, recurrent pregnancy loss
- contraindications: pregnancy, pelvic infection

**Table 15. Typical and Atypical Findings on a Sonohysterogram**

Finding	Typical	Atypical
<b>Polyps</b>	A well-defined, homogenous, polypoid lesion isoechoic to the endometrium with preservation of the endometrial-myometrial interface	Atypical features include cystic components, multiple polyps, broad base, hypoechogenicity or heterogeneity
<b>Leiomyoma</b>	Well-defined, broad-based, hypoechoic, solid masses with shadowing. Overlying layer of endometrium is echogenic and distorts the endometrial-myometrial interface	Pedunculation or multilobulated surface
<b>Hyperplasia and Cancer</b>	Diffuse echogenic endometrial thickening without focal abnormality, although focal lesions can occur. Endometrial cancer is typically a diffuse process, but early cases can be focal and appear as a polypoid mass	
<b>Adhesions</b>	Mobile, thin, echogenic bands that cut across the endometrial cavity	Thick, broad-based bands that can completely obliterate the endometrial cavity, as in Asherman's syndrome

## Adrenal Mass

- imaging modality: most often identified on CT scan, can use MR to distinguish benign from malignant masses

**Table 16. Adrenal Mass Findings on CT and MRI**

Factors	Adrenocortical Adenoma	Adrenocortical Carcinoma	Pheochromocytoma	Metastasis
Diameter (CT)	Usually $\leq 3$ cm	Usually $\geq 4$ cm	Usually $> 3$ cm	Variable around $< 3$ cm
Shape (CT)	Smooth margins and round/oval	Irregular with unclear margins	Round/oval with clear margins	Oval/irregular with unclear margins
Texture (CT)	Homogenous	Heterogeneous with mixed densities	Heterogeneous with cystic areas	Heterogeneous with mixed densities
Vascularity (CT)	Not highly vascular	Usually vascular	Usually vascular	Usually Vascular
Washout of Contrast Medium on CT	$\geq 50\%$ at 10 min	$< 50\%$ at 10 min	$< 50\%$ at 10 min	$< 50\%$ at 10 min
Growth	Stable or very slow ( $< 1$ cm/yr)	Usually rapid ( $> 2$ cm/yr)	Slow (0.5-1 cm/yr)	Variable
Other Findings	None	Necrosis, calcifications, and hemorrhage	Hemorrhage	Occasionally hemorrhage
MRI on T2 weighted imaging	Isointense in relation to liver	Hyperintense in relation to liver	Markedly hyperintense in relation to liver	Hyperintense in relation to liver

## Neuroradiology

### Modalities

- CT is the modality of choice for most neuropathology; even under circumstances when MRI is preferred, CT is frequently the initial study because of its speed, availability and lower cost
- CT is preferred for
  - acute head trauma: CT is best for visualizing "bone and blood"; MRI is used in this setting only when CT fails to detect an abnormality in the presence of strong clinical suspicion
  - acute stroke: MRI ideal, CT most frequently used
  - suspected subarachnoid or intracranial hemorrhage
  - meningitis: rule out mass effect (e.g. cerebral herniation, shift) prior to lumbar puncture
  - tinnitus and vertigo: CT and MRI are used in combination to detect bony abnormalities and CN VIII tumours, respectively



#### Modality Based on Neuropathology Presentation

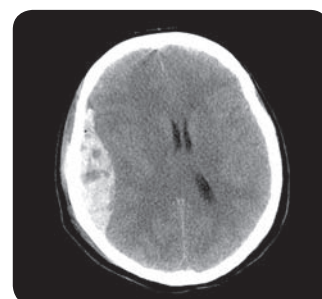
- Cognitive decline = CT
- Cord compression = MRI
- Decreased LOC = CT
- Fish bone/other swallowed foreign body = CT
- LBP, radiculopathy = MRI
- Multiple sclerosis = MRI
- Neck infection = CT
- Orbital infection = CT
- R/O bleed = CT
- R/O aneurysm = CTA, MRA
- Seizure = CT
- Sinusitis = CT
- Stroke = CT, MRI
- Trauma = CT
- Weakness, systemically unwell = CT



#### DDx for Ring Enhancing Lesion on CT with Contrast

- MAGICAL DR**
- \*Metastases
  - \*Abscess
  - \*Glioblastoma (high grade astrocytoma)
  - Infarct
  - Contusion
  - AIDS
  - Lymphoma
  - Demyelination
  - Resolving hematoma

[\*the 3 most common Dx's]



**Figure 23. Epidural hematoma**

### Skull Films

- rarely performed as CT is the modality of choice
- indications: include screening for destructive bony lesions (e.g. metastases), metabolic disease, skull anomalies, post-operative changes and confirmation of hardware placement, skeletal surveys
- generally not indicated for non-penetrating head trauma

### CT

- excellent study for evaluation of bony abnormalities
- often done first without and then with intravenous contrast to show vascular structures or anomalies
- vascular structures and areas of blood-brain barrier impairment are opaque (e.g. hyperattenuating or white/show enhancement) with contrast injection
  - when in doubt, look for circle of Willis or confluence of sinuses to determine presence of contrast enhancement
- posterior fossa can be obscured by extensive bony artifact
- rule out skull fracture, epidural hematoma (lenticular shape), subdural hematoma (crescentic shape), subarachnoid hemorrhage, space occupying lesion, hydrocephalus, and cerebral edema
- multiplanar imaging can be performed with newer generation of multidetector CT scanners

### Myelography

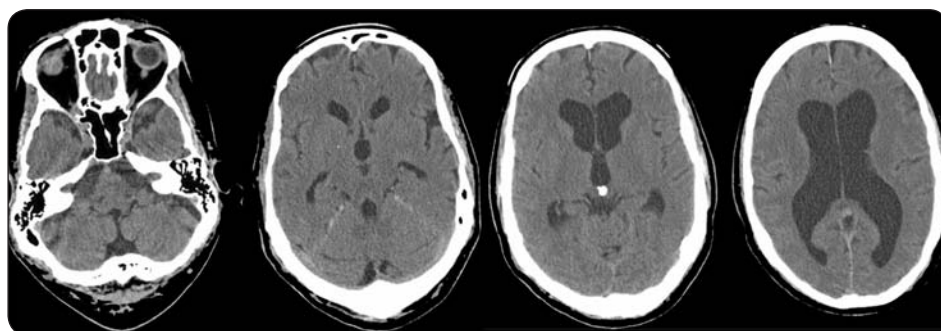
- introduction of water-soluble, low-osmotic-contrast media into subarachnoid space using lumbar puncture followed by x-ray or CT scan
- indications: excellent study for disc herniations, traumatic nerve root avulsions, patients with contraindication to MRI

### MRI

- indications: shows brain and spinal soft tissue anatomy in fine detail, clearly distinguishes white from grey matter (especially T1-weighted series), multiplanar reconstruction helpful in pre-op assessment

### Cerebral Angiography/CT Angiography/MR Angiography

- indications: evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissection
- conventional digital subtraction angiography (DSA) remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (femoral) puncture; catheter manipulation has risk of vessel injury (e.g. dissection, occlusion, vasospasm, emboli)
- MR angiography (MRA) methods (phase contrast, time of flight, gadolinium-enhanced) and CT angiography (CTA) are much less invasive without actual risk to intracranial or neck vessels
- MRA and CTA are often used first as 'screening tests' for the assessment of subarachnoid hemorrhage, vasospasm, aneurysms



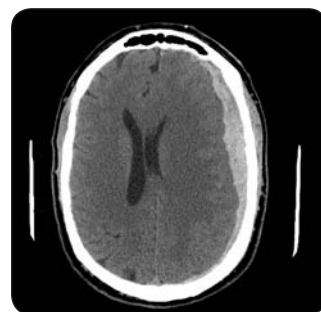
**Figure 28. Hydrocephalus:** ventricular dilatation (may see periventricular low attenuation due to transependymal CSF flow)

**Table 17. Two Types of Hydrocephalus**

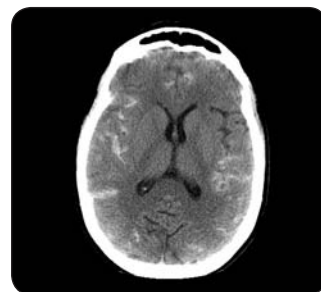
Type	Cause
Communicating/extra-ventricular	Obstruction distal to the ventricles e.g. at the level of the arachnoid granulations; imaging shows all ventricles dilated
Non-communicating	Obstruction within the ventricular system e.g. mass obstructing the aqueduct or foramen of Monro; imaging shows dilatation of ventricles proximal to the lesion

### Nuclear Medicine

- SPECT using  $^{99m}\text{Tc}$ -exametazime (HMPAO) and  $^{99m}\text{Tc}$ -bicisate (ECD) imaging assesses cerebral blood flow by diffusing rapidly across the blood brain barrier and becoming trapped within cells
- $^{18}\text{F}$ FDG PET imaging assesses cerebral metabolic activity



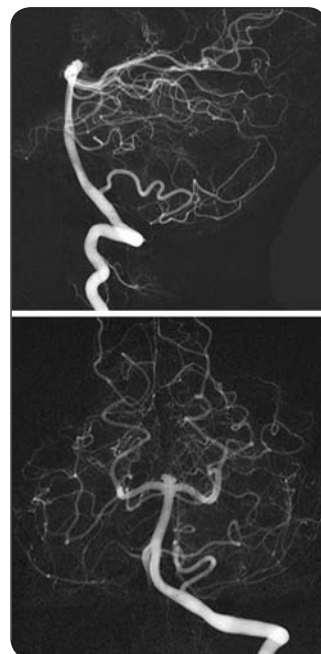
**Figure 24. Subdural hematoma**



**Figure 25. Subarachnoid hemorrhage**



**Figure 26. Intraparenchymal hemorrhage**



**Figure 27. Vertebrobasilar circulation**



## Approach to CT Head

- think anatomically, work from superficial to deep
- scan: confirm that the imaging is of the correct patient, whether contrast was used, if the patient is aligned properly, if there is artifact present
- skin/soft tissue: examine the soft-tissue superficial to the skull, looking for thickening suggestive of hematoma or edema; also investigate: ear, orbital contents (globe, fat, muscles), parotid, muscles of mastication (masseter, temporalis, pterygoids), visualized pharynx
- bone and airspace (use the bone window): check calvarium, visualized mandible, visualized C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for opacity that may suggest fluid, pus, blood, tumour, or fracture
- dura and subdural space: look for crescent-shaped hyperdensity in the subdural space as evidence of subdural hematoma; look for a lentiform hyperdensity in epidural space as evidence of epidural hematoma; check symmetry of dural thickness, where increased thickness may suggest the presence of blood
- parenchyma: look for symmetry of the parenchyma for evidence of midline shift; look for poor contrast between grey and white matter as evidence of possible infarction, tumour, edema, infection, or contusion; look for hyperdensities in the parenchyma suggestive of enhancing lesions, intracerebral hemorrhage, or calcification; central grey matter nuclei should be visible, including globus pallidus, putamen, and internal capsule, otherwise suspect infarct, tumour, or infection
- ventricles/sulci/cisterns: examine position of ventricles for evidence of midline compression/shift; look for hyperdensities in the ventricles indicative of ventricular/subdural hemorrhage; look at ventricular size for evidence of hydrocephalus; obliteration of sulci may suggest presence of edema causing effacement, possible blood filling in the sulci, or tumour; cistern hyperdensities may suggest blood, pus, or tumour



### Approach to the CT Head

**Some** = Scan  
**Sore** = Skin/Soft Tissue  
**Brains** = Bone/Airspace  
**Demonstrate** = Dura/Subdural space  
**Pushed** = Parenchyma  
**Ventricles** = Ventricles/Sulci/Cisterns



Transient ischemic attacks are not associated with radiological findings.



### Early Signs of Brain Infarction at CT: Observer Reliability and Outcome after Thrombolytic Treatment – Systematic Review

*Radiology* 2005;235:444-453

**Study:** Systematic review of 15 studies between 1990-2003 that investigated inter-observer agreement of early CT signs of acute ischemic stroke, and prognostic value of early CT signs in patient outcome. There was a median of 30 CTs and 6 raters per study.

**Patients:** 3468 adult patients who underwent CT within 6 h of stroke.

**Main Outcome:** Degree of inter-observer agreement between stroke signs on CT, and risk of death or dependency (using validated stroke scales) based on CT signs used after 1-3 mo.

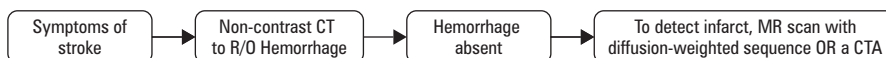
**Results:** Prevalence of all early infarction signs was  $61\% \pm 21$ , and interobserver agreement was 0.14-0.78 (K statistic) for any early infarct sign. Average sensitivity of detecting early ischemic stroke was 66% (range 20%-87%) and average specificity was 87% (range 56%-100%). Experience improved detection, but knowledge of patient history did not. An increased risk of poor outcome (death or dependency) was associated with any early infarction sign, with an odds ratio of 3.11 (95%CI, 2.77-3.49).

**Conclusion:** Further work is required to determine which signs are most reliably detected and whether any early infarction sign should influence decisions concerning thrombolysis.

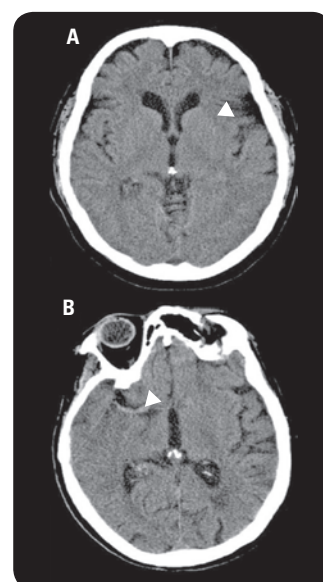
## Selected Pathology

- see [Neurosurgery](#), NS4-23 for intracranial mass lesions
- see [Neurosurgery](#), NS30-35 and [Plastic Surgery](#), PL28 for head trauma
- see [Emergency Medicine](#), ER7 for vertebral trauma
- see [Neurosurgery](#), NS24-29 and [Orthopedics](#), OR21 for degenerative spinal abnormalities

### Cerebrovascular Disease (see [Neurology](#), N43-46 and [Neurosurgery](#), NS18-23)



- pathogenesis of stroke: see [Neurology](#), N43
- best imaging modality ischemic strokes usually cause infarcts which can be detected by both CT and MR
- findings of infarction:
  - early changes
    - ♦ CT
      - usually normal within 6 h of infarction
      - edema (loss of grey-white matter differentiation – “insular ribbon” sign, effacement of sulci, mass effect)
      - within 24 h, development of low-density, wedge-shaped area of infarction extending to periphery (correlating to vascular territory distal to affected artery)
      - refer to Functional Neuroanatomy software online ([www.torontonotes.ca](http://www.torontonotes.ca))
      - in case of ischemic stroke, may see hyperattenuating (bright) artery (hyperdense MCA sign) representing intravascular thrombus or embolus
      - in case of hemorrhagic stroke or transformation (common in basal ganglia and cortex), may see bright acute blood surrounded by edema
    - ♦ MRI
      - edema with high signal on T2-weighted images and FLAIR image (loss of grey-white matter differentiation, effacement of sulci, mass effect)
      - diffusion-weighted image (DWI) shows acute high signal changes demonstrating restricted movement of water indicative of cytotoxic edema. DWI usually indicates stroke damage before CT
      - apparent diffusion coefficient (ADC) image shows low signal intensity in acute ischemia (nadir 3-5 d, returns to baseline 1-4 wk)
  - subacute changes on CT and MRI
    - ♦ edema and mass effect more prominent
    - ♦ gyral enhancement with contrast indicative of blood-brain barrier breakdown
  - chronic changes on CT and MRI
    - ♦ encephalomalacia (parenchymal volume loss) with dilatation of adjacent ventricles



**Figure 29. CT images of early infarct: (A) absence of left insular ribbon (B) hyperdense artery**

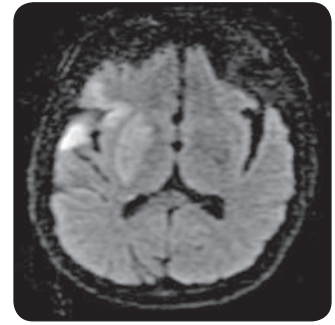
- carotid artery disease
  - best imaging modality: Duplex Doppler U/S
  - other modalities: MR angiography or CT angiography if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)

### Multiple Sclerosis (MS) (refer to [Neurology](#), N46)

- best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
- findings:
  - characteristic lesion on MRI is cerebral or spinal plaque
  - plaques typically found in periventricular region, corpus callosum (arranged at right angles to the corpus callosum), centrum semiovale, and to a lesser extent in deep white matter structures and basal ganglia
  - “Dawson’s fingers” refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  - plaques usually have ovoid appearance, hyperintense on T2 and hypointense on T1
  - conventional T2 may underestimate plaque size and overall plaque burden – advanced techniques (diffusion tensor imaging and magnetic resonance spectroscopy) can be of use
  - perivascular and interstitial edema may be prominent
- acute vs. chronic
  - acute lesions: larger, ill-defined margins and become smaller with sharper margins with resolution of edema and inflammation present at time of acute plaque formation
  - gadolinium enhancing lesions on T1-weighted MRI: accumulation of gadolinium in plaques is associated with new or newly active plaques and with pathologically confirmed acute inflammation in MS; gadolinium enhancement is transient and can persist up to 8 wk in acute plaques (persistence of enhancement should caution against diagnosis of MS)
  - enhancement patterns: concentric ring-enhancing lesions with central contrast pallor arise in previously damaged areas or areas of accelerated local inflammation; ring-enhancing lesions weakly predict the development of persisting hypointense lesions on T1 MRI and are thought to be related to accelerated disease activity and extensive tissue damage, marking inflammation associated with aggressive disease
  - most MS lesions are isointense to white matter on T1-weighted MRI, some are hypointense or “black holes” (especially in the supratentorial region). Nearly half of black holes revert to normal in a few months, presumably due to remyelination and resolution of edema. Persistent black holes may be markers of severe demyelination and axonal loss
  - spinal cord lesions typical of MS:
    - ♦ little or no cord swelling
    - ♦ unequivocal hyperintensity on T2-weighted sequences
    - ♦ size at least 3 mm but less than 2 vertebral segments in length
    - ♦ occupy only part of the cord in cross-section
    - ♦ focal (i.e. clearly delineated and circumscribed on T2-weighted sequences)

### CNS Infections

- **leptomeningitis**
  - pathogenesis: inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via organisms gaining access across areas not protected by the blood brain barrier (choroid plexus or circumventricular organs)
    - ♦ pathogens include: *S. pneumoniae*, *H. influenza*, *N. meningitidis*, *L. monocytogenes*
  - best imaging modality: best visualized with MRI (T2-weighted/FLAIR) over CT
  - findings:
    - ♦ meningeal enhancement (following the gyri/sulci, and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
    - ♦ a normal MRI does not rule out leptomeningitis
- **herpes simplex encephalitis** (see [Infectious Diseases](#), ID20)
  - pathogenesis: inflammation of the brain parenchyma secondary to HSV infection, asymmetrically affects the limbic regions of the brain – temporal lobes, orbitofrontal region, insula, and cingulate gyrus
  - best imaging modality: best imaged with MRI (T1- and T2-weighted imaging)
  - findings:
    - acute (within 4-5 d): high intensity lesions on T2 MRI in temporal and inferior frontal lobes, asymmetric
    - strongly suggestive of HSV encephalitis
    - DDx: infarct, tumour, status epilepticus, limbic encephalitis
    - ♦ CT may show low density in temporal lobe and insula; rarely basal ganglia involvement
    - ♦ long term may show parenchymal loss to affected areas

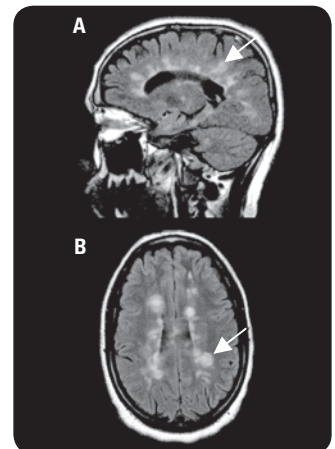


**Figure 30. Diffusion weighted imaging of patient with normal CT: right frontotemporal infarct**

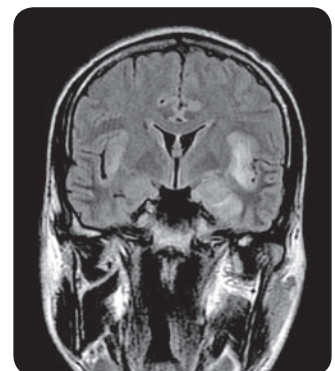


#### DDx Suspected MS lesion

- Vasculopathy: ischemia, vasculitis, hypertension, migraine
- Demyelinating disease: progressive multifocal leukoencephalopathy, age-related
- Inflammatory process: sarcoid, lyme, primary/metastatic cancer



**Figure 31. T2-weighted FLAIR: (A) sagittal (B) axial images of multiple sclerosis with periventricular “Dawson’s Fingers”**



**Figure 32. T2-weighted (FLAIR) coronal image of HSV encephalitis affecting temporal lobes**



- **cerebritis/cerebral abscess**

- pathogenesis: an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms, commonly located in the distribution of the middle cerebral artery
  - ♦ pathogens include: *S. aureus* (often in IVDU, nosocomial), GN bacteria, *Streptococcus*, *Bacteroides*
- best imaging modality: MRI including diffusion (DWI) imaging series – an abscess will be DWI positive; CT is still used as a viable alternative but overall MRI > CT
- findings according to one of four stages of abscess formation:
  - ♦ early cerebritis (1-3 d): inflammatory infiltrate with necrotic centre, low intensity on T1, high intensity on T2
  - ♦ late cerebritis (4-9 d): ring enhancement may be present
  - ♦ early capsule (10-13 d): ring enhancement
  - ♦ late capsule (14 d or greater): well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperdensity on T2

## Musculoskeletal System (MSK)

### Modalities

#### Plain Film/X-Ray

- usually initial study used in evaluation of bone and joint disorders
- indications: fractures and dislocations, arthritis, assessment of malalignment, assessment of orthopedic hardware, initial assessment of bone tumours
- minimum of two films orthogonal to each other (usually AP and lateral) to rule out a fracture
- image proximal and distal joints (particularly important with paired bones, e.g. radius/ulna)
- not very effective in evaluating soft tissue injury
- advantages: fast, inexpensive, readily available, reproducible

#### CT

- evaluation of fine bony detail
- indications: assessment of complex, comminuted, intra-articular or occult fractures including distal radius, scaphoid, skull, spine, acetabulum, calcaneus, and sacrum
- evaluation of soft tissue calcification/ossification
- advantages: fast, reproducible, excellent bone evaluation, and spatial resolution
- disadvantages: radiation dose, relatively poor soft tissue characterization in comparison with U/S and MRI

#### MRI

- indications: evaluation of internal derangement of joints (ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses
- advantages: excellent soft tissue contrast, multiplanar imaging, no radiation
- disadvantages: long imaging times, expensive, claustrophobia, contraindications (e.g. pacemakers, orbital metallic bodies), artifact around metal hardware

#### Ultrasound

- indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection of soft tissue masses and to determine whether cystic or solid, detection of foreign bodies, ultrasound guided biopsy and injections
- Doppler determines vascularity of structures
- advantages: good soft tissue evaluation, easy contralateral comparison, dynamic imaging
- disadvantages: operator dependent, poor for bone evaluation

#### Nuclear Medicine (Bone Scintigraphy)

- determine the location and extent of bony lesions
- <sup>99m</sup>Tc-methylene diphosphonate (MDP) localize to areas of increased bone turnover or calcification – growth plate in children, tumours, infections, fractures, metabolic bone disease (e.g. Paget's), sites of reactive bone formation, and periostitis
- very sensitive, not specific (trauma, infection, inflammation look similar)

### Approach to Interpretation of Bone X-Rays

- identification: name, MRN, age of patient, type of study, region of investigation
- soft tissues: swelling, calcification/ossification
- joints: alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, and symmetry of affected joint
- bone: periosteum, cortex, medulla, trabeculae, density, articular surfaces, bone destruction, bone production, appearance of the edges or borders of any lesions (Figure 34)



#### Approach to Fractures

##### BONES

Black lines/Breaks in cortex

Osteoporosis

Not aligned (angulation, translation, rotation)

Extension into joint

Soft tissue swelling/Sclerosis (past fracture)

See [Orthopedics](#), OR5

## Trauma

### Fracture/Dislocation

- description of fractures
- site of fracture (bone, region of bone, intra-articular vs. extra-articular)
- pattern of fracture line (simple vs. comminuted)
- displacement (distal fragment with reference to the proximal fragment)
- soft tissue involvement (calcification, gas, foreign bodies)
- type of fracture (stress vs. pathologic)
- for specific fracture descriptions and characteristics of fractures, see [Orthopedics](#), OR5

## Arthritis

### Radiographic Hallmarks of OA

- joint space narrowing – typically non-uniform
- subchondral sclerosis
- subchondral cyst formation
- osteophytes

### Radiographic Hallmarks of RA

- joint space narrowing – typically uniform
- soft tissue swelling
- erosions
- periarticular osteopenia

## Bone Tumour

### Approach

- metastatic tumours to bone are much more common than primary bone tumours, particularly if age >40 yr
  - diagnosis usually requires a biopsy if primary not located
  - few benign tumours/lesions have potential for malignant transformation
  - MRI is good for tissue delineation and preoperative assessment of surrounding soft tissues, neurovascular structures, and medullary/marrow involvement
  - plain film is less sensitive than other modalities but useful for assessing aggressiveness and constructing differential diagnosis

### Considerations and Tumour Characteristics

- age – most common tumours by age group
  - <1 yr of age: metastatic neuroblastoma
  - 1-20 yr of age: Ewing's tumour in tubular bones
  - 10-30 yr of age: osteosarcoma and Ewing's tumour in flat bones
  - >40 yr of age: metastases, multiple myeloma, and chondrosarcoma
- multiplicity: metastases, myeloma, lymphoma, fibrous dysplasia, enchondromatosis
- location within bone
  - epiphysis: giant cell tumour, chondroblastoma, geode, eosinophilic granuloma, infection
  - metaphysis: simple bone cyst, aneurysmal bone cyst, enchondroma, chondromyxoid fibroma, nonossifying fibroma, osteosarcoma, chondrosarcoma
  - diaphysis: fibrous dysplasia, aneurysmal bone cyst, brown tumours, eosinophilic granuloma, Ewing's sarcoma
- expansile
  - aneurysmal bone cyst, giant cell tumour, enchondromas, brown tumours, metastases (especially renal and thyroid), plasmacytoma
- matrix mineralization
  - chondroid (popcorn calcification) or osseous
- margin/zone of transition: area between lesion and normal bone
- cortex: intact, disturbed
- periosteal reaction
- soft tissue mass
- see Figure 34 and Table 18

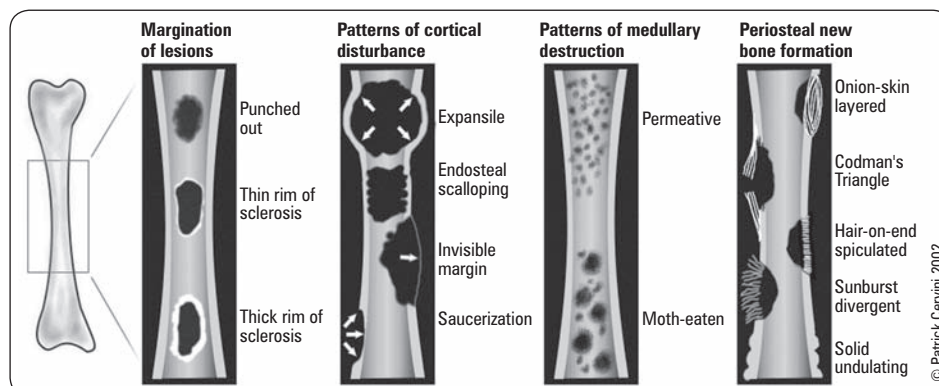


Figure 34. Radiographic appearance of bone remodelling and destruction processes



### Types of Fractures

- Transverse
- Oblique
- Spiral
- Avulsion
- Impacted



### Types of Displacements

- Translation
- Angulation
- Rotation
- Impaction
- Dislocation



Figure 33. X-ray of first carpometacarpal joint: normal image (left side) and osteoarthritis (right side) with joint space narrowing and subchondral sclerosis



### Benign Lesions which may have Aggressive Features

- Osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Myositis ossificans



### Periosteal Reaction

- "Onion skinning" = Ewing's sarcoma
- "Sunburst", "hair on end" = osteosarcoma
- "Codman's triangle" = osteosarcoma, Ewing's sarcoma, subperiosteal abscess



Lytic = decreased density  
Sclerotic = increased density

**Table 18. Characteristics of Benign and Malignant Bone Lesions**

Benign	Malignant
Thin sclerotic margin/sharp delineation of lesion	Poor delineation of lesion – wide zone of transition
Overlying cortex intact	Loss of overlying cortex/bony destruction
No or simple periosteal reaction	Periosteal reaction
No soft tissue mass	Soft tissue mass
Note: for specific bone tumours see <a href="#">Orthopedics</a> , OR42	

**Metastatic Bone Tumours**

- all malignancies have potential to metastasize to bone
- metastases are 20-30x more common than primary bone tumours
- metastasis can cause a lytic or a sclerotic reaction when seeding to bone
- when a primary malignancy is first detected, a bone scan is often part of the initial work-up
- may present with pathological fractures or pain
- biopsy or determination of primary is the only way to confirm the diagnosis
- most common metastatic bone tumours: breast, prostate, lung, see [Orthopedics](#), OR45

**Table 19. Characteristic Bone Metastases of Common Cancers**

Lytic	Sclerotic	Expansile	Peripheral
Breast	Prostate	Thyroid	Kidney
Lung	Breast	Renal	Lung
Thyroid	Lymphoma		Melanoma
Kidney	Lung		(KLM: flies to the periphery)
Multiple myeloma	Bowel		
	Medulloblastoma		
	Treated tumours		

## Infection

**Osteomyelitis**

- MRI is the imaging modality of choice for demonstrating bone, bone marrow, and soft tissue abnormalities
- $^{99m}\text{Tc}$ , followed by  $^{111}\text{In}$  labeled white cell scan or gallium radioisotope scan
- plain film
  - visible 8-10 d after process has begun
  - osteomyelitic changes on plain film
    - ♦ soft tissue swelling
    - ♦ local periosteal reaction
    - ♦ pockets of air (from anaerobes) may be seen in the tissues, may also suggest necrotizing fasciitis
    - ♦ mottled and nonhomogeneous with a classic “moth-eaten” appearance
    - ♦ cortical destruction

**Bone Abscess**

- overlying cortex has periosteal new bone formation
- sharply outlined radiolucent area with variable thickness in zone of transition
- variable thickness periosteal sclerosis
- sequestrum: a piece of dead bone within a Brodie’s abscess
- a sinus tract or cloaca may communicate between the abscess through the cortex to the surface of the bone

## Metabolic Bone Disease

**Osteoporosis**

- reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
- dual energy x-ray absorptiometry (DEXA): gold standard for measuring bone mineral density
  - T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - ♦ osteopenia:  $-2.5 < \text{T-score} < -1$
    - ♦ osteoporosis:  $\text{T-score} \leq -2.5$
  - Z-score: the number of standard deviations from the age-matched mean
  - risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy



Diagnostic sensitivity of DEXA highest when BMD measured at lumbar spine and proximal femur.

- appearance on plain film
  - osteopenia: reduced bone density on plain films
    - ♦ may also be seen with osteomalacia, hyperparathyroidism, and disuse
  - compression of vertebral bodies
  - biconcave vertebral bodies ("codfish" vertebrae)
  - long bones have appearance of thinned cortex and increased medullary cavity
  - look for complications of osteoporosis
    - ♦ e.g. insufficiency fractures: hip, vertebrae, sacrum, pubic rami
- see [Endocrinology](#), E42

### Osteomalacia/Rickets

- reduction in bone mineral density, usually due to vitamin D deficiency, resulting in softening and bowing of long bones
- similar to osteoporosis, initial radiological appearance of osteopenia (coarse and poorly defined bone texture)
- "fuzzy", ill-defined trabeculae
- Looser's zones (pseudofracture)
  - characteristic radiologic feature
  - fissures or clefts at right angles to long bones and extending through cortex
  - DDx: osteomalacia, chronic renal disease, fibrous dysplasia, hyperthyroidism, Paget's, osteodystrophy, X-linked hypophosphatemia



#### Osteoporosis

Reduced amount of bone

#### OsteoMalacia

Normal amount of bone, but reduced mineralization of normal osteoid

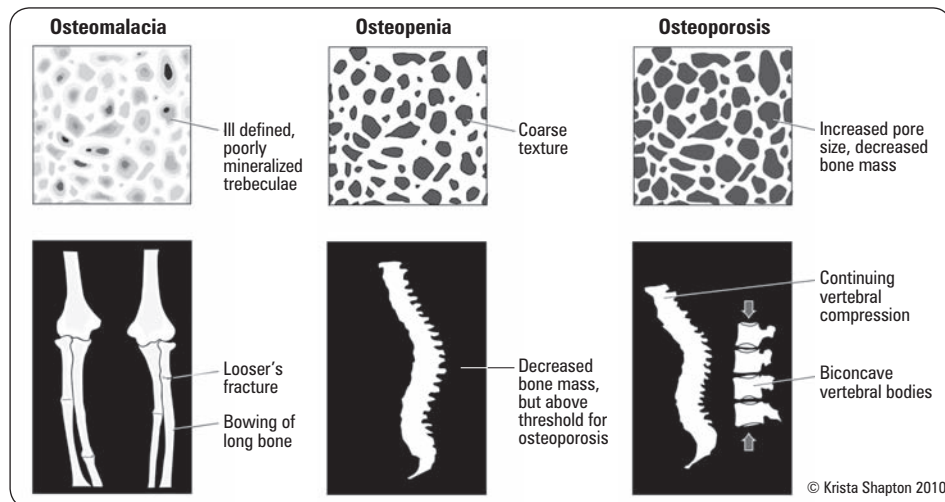


Figure 35. Osteomalacia, osteopenia and osteoporosis

### Hyperparathyroidism

- most common cause is renal failure (secondary hyperparathyroidism)
- chondrocalcinosis
  - calcium crystal deposition in hyaline cartilage or fibrocartilage (including arteries and peri-articular soft tissue)
  - resorption of bone typically in hands (subperiosteal and at tufts), SI joints (subchondral), skull ("salt and pepper" appearance), osteoclastoma (brown tumours)
  - "rugger jersey spine": band-like osteosclerosis at superior/inferior margins of vertebral bodies
- see [Endocrinology](#), E38



### Paget's Disease

- abnormal remodeling involving single or multiple bones – especially skull, spine, pelvis
- 3 phases: 1st phase = lytic, 2nd phase = mixed (lytic/sclerotic), 3rd phase = sclerotic
- features
  - coarsening of the trabeculae with bone expansion
  - bone softening/bowing
  - bone scan will reveal high activity, especially at bone ends
  - thickened cortex
- see [Endocrinology](#), E46



# Nuclear Medicine



## Brain

- $^{99m}\text{Tc}$ -exametazime (HMPAO) and  $^{99m}\text{Tc}$ -bicisate (ECD) imaging to assess cerebral blood flow, taken up in cortical and subcortical grey matter; used for dementia, traumatic brain injury and to a lesser extent vasculitis, neuropsychiatric disorders and stroke
- PET imaging assesses metabolic activity by using  $^{18}\text{F}$ FDG
- CSF imaging, intrathecal administration of  $^{111}\text{In}$  DTPA to evaluate CSF leak or to differentiate normal pressure hydrocephalus from other causes of hydrocephalus
- ventricular shunt evaluation for obstruction (most commonly ventricular peritoneal) with  $^{99m}\text{Tc}$  or  $^{111}\text{In}$ -DTPA

## Thyroid

### Radioactive Iodine Uptake (see [Endocrinology](#), E22)

- index of thyroid function (trapping and organification of iodine)
- radioactive  $^{131}\text{I}$  or  $^{123}\text{I}$  given PO to fasting patient
- measure percentage of administered iodine taken up by thyroid
- increased RAIU: toxic multinodular goiter, toxic adenoma, Graves' disease
- decreased RAIU: subacute thyroiditis, late Hashimoto's disease, hormone suppression
- falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed)



### Thyroid Imaging (Scintiscan)

- $^{99m}\text{Tc}$  pertechnetate IV or radioactive iodine ( $^{123}\text{I}$ )
- provides functional anatomic detail
- hot (hyperfunctioning) lesions
  - adenoma, toxic multinodular goiter
  - usually benign, cancer very unlikely (less than 1%)
- cold (hypofunctioning) lesions
  - cancer must be considered until biopsy negative even though only 6-10% are cancerous
- isointense lesions
  - cancer must be considered as an isointense lesion may represent cold nodules superimposed on normal tissue
  - if cyst suspected, correlate with U/S
- serum thyroglobulin to detect recurrent thyroid cancer post-treatment

### Radioiodine Ablation

- $^{123}\text{I}$  for Graves' disease, multinodular goiter, thyroid cancer

## Respiratory

### V/Q Scan

- examine areas of lung in which ventilation and perfusion do not match
- ventilation scan
  - patient breathes radioactive gas ( $^{99m}\text{Tc}$ -DTPA,  $^{133}\text{Xe}$ , Technegas) through a closed system, filling alveoli proportionally to ventilation
  - ventilation scan defects indicate: airway obstruction, chronic lung disease, bronchospasm, tumour mass obstruction
- perfusion scan
  - radiotracer injected IV ( $^{99m}\text{Tc}$ -MAA) → trapped in pulmonary capillaries (1 in 1500 arterioles occluded) according to blood flow
  - gives a map of pulmonary circulation
  - relatively contraindicated in severe pulmonary HTN and right-to-left shunt
- with PE
  - areas of lung are well ventilated but not perfused (unmatched defect)
  - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
  - reported as high probability, intermediate, low, very low, or normal
  - V/Q scans for PE have been largely replaced by CT scan with contrast (see [Respirology](#), R18)
- not valid for assessment of PE when patients have intrinsic lung diseases and ventilatory problems



#### V/Q Scan

For PE investigation: normal scan makes PE unlikely.  
Probability of PE: high 80-100%, intermediate 20-80%, low <20%, very low <10%.



#### Ventilation Scan Defects indicate:

Airway obstruction, chronic lung disease, bronchospasm, tumour mass obstruction.



#### Perfusion Scan Defects indicate:

Reduced blood flow due to PE, COPD, asthma, bronchogenic carcinoma, inflammatory lung diseases (pneumonia, sarcoidosis), mediastinitis, mucous plug, vasculitis.

## Cardiac

### Myocardial Perfusion Scanning

- for investigation of angina, atypical chest pain, coronary artery disease, and follow-up post-bypass
- thallium-201 (a radioactive analogue of potassium),  $^{99m}\text{Tc}$  sestamibi (MIBI), or  $^{99m}\text{Tc}$  tetrofosmin
- injected at peak exercise (physical stress) or after persantine challenge (vasodilator) and again later at rest
- persistent defect (at rest and stress) suggests infarction; reversible defect (only during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- see [Cardiology and Cardiovascular Surgery](#), C10 for more details

### Radionuclide Ventriculography

- $^{99m}\text{Tc}$  tagged to red blood cells
- first pass through right ventricle  $\rightarrow$  pulmonary circulation  $\rightarrow$  left ventricle; provides information about RV function
- cardiac MUGA scan (Multiple GAted acquisition scan) sums multiple cardiac cycles
  - evaluation of LV function
  - images are obtained by gating (synchronizing) the count acquisitions to the ECG signal
  - MUGA scan can be used to study the function of the heart at a particular stage of contraction
- provides information on ejection fraction (normal = 50-65%), ventricular volume, and wall motion



Active uptake of radiolabel by myocardium is proportional to regional blood flow.



Persistent defect (at rest and stress) suggests infarction; reversible defect (only during stress) suggests ischemia.



**MUGA Scan** can be used to study the function of the heart at a particular stage of contraction. Superior to ECHO only in its reproducibility in EF measurement (precise).

## Abdomen and Genitourinary System

### HIDA (Hepatobiliary IminoDiacetic Acid) Scan

- IV injection of  $^{99m}\text{Tc}$ -disofenin (DISIDA) or  $^{99m}\text{Tc}$ -mebrofenin (BRIDA) which is bound to protein, taken up, and excreted by hepatocytes into biliary system
- can be performed in non-fasting state but prefer NPO after midnight
- gallbladder visualized when cystic duct is patent, usually seen by 30 min to 1 h
- if gallbladder is not visualized, suspect obstructed cystic duct (acute or chronic cholecystitis)
- acute cholecystitis: no visualization of gallbladder at 4 h or after administration of morphine at 30 min
- chronic cholecystitis: no visualization of gallbladder at 1 h but seen at 4 h or after morphine administration
- differential diagnosis of obstructed cystic duct: acute cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting less than 4 h or more than 24 h
- filling of gallbladder rules out cholecystitis (<1% probability)
- assess bile leaks post-operatively

### RBC Scan

- IV injection of radiotracer with sequential images of the abdomen ( $^{99m}\text{Tc}$  RBCs)
- GI bleed
  - if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed, look for a change in shape and location on sequential image
  - if bleeding acutely at >0.5 mL/min, use angiography (more specific)
  - RBC scan is more sensitive for lower GI bleed
- liver lesion evaluation
  - hemangioma has characteristic appearance: cold early, fills in later

### Renal Scan

- see [Genitourinary System](#), MI16

### Scrotal Scintigraphy

- scrotal scintigraphy has now been replaced by Doppler U/S



## Bone



### Bone Scan

- isotopes
  - $^{99m}\text{Tc}$ -diphosphonate
    - triphasic bone scan: flow → blood pool → delayed bone images
    - uptake can distinguish bone vs. soft tissue infection and septic arthritis vs. osteomyelitis vs. peripheral cellulitis
    - acute osteomyelitis: increased activity in flow, blood pool, and delayed bone images; usually does not cross joint
    - septic arthritis and cellulitis: increased activity in blood pool and normal or slightly increased activity in delayed images; may cross joint
  - $^{111}\text{In}$  WBC: tracks the active migration of the WBC, more specific for infection
  - $^{67}\text{Ga}$  citrate: may see uptake in some tumours, also more specific for infection
- radioactive tracer binds to hydroxyapatite of bone matrix
- increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
- indications:
  - bone pain of unknown origin
  - AVN
  - suspected malignancy
  - staging malignancy (cancer of breast, prostate, kidney or lung)
  - follow up after treatment
  - detection and follow up of primary bone disease
  - assessment of skeletal trauma
  - detection of soft tissue calcification
  - renal failure
- differential diagnosis of positive bone scan:
  - bone metastases from breast, prostate, lung, thyroid
  - primary bone tumour
  - arthritis
  - fracture
  - infection
  - anemia
  - Paget's disease
- multiple myeloma: typically normal or cold (false negative); need a skeletal survey
- "superscan": increased bone uptake and poor renal uptake due to diffuse metastases or metabolic causes (renal osteodystrophy)

## Interventional Radiology

### Vascular Procedures

#### Angiography

- injection of contrast material through a catheter placed directly into an artery or vein to delineate vascular anatomy
- catheter can be placed into a large vessel (e.g. aorta, vena cava) for a "flush" or selectively placed into a branch vessel for more detailed examination of smaller vessels and specific organs
- indications: diagnosis of primary occlusive or stenotic vascular disease, aneurysms, coronary, carotid and cerebral vascular disease, PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (EVAR, thrombolysis, stenting and angioplasties)
- complications: puncture site hematoma, infection, pseudoaneurysm, AV fistula, dissection, thrombosis, embolic occlusion of a distal vessel
- significant complications occur in <5% of patients
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (colour Doppler U/S, CT angiography and MR angiography)
- see *Neuroradiology*, MI18

#### Percutaneous Transluminal Angioplasty (PTA) and Stents

- introduction and inflation of a balloon into a stenosed vessel to restore distal blood supply
- common alternative to surgical bypass grafting with five year patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary and carotid artery stenoses are amenable to treatment



On U/S, veins are compressible, arteries are not.



#### Thrombolytic Therapy for Pulmonary Embolism

*Cochrane DB Syst Rev 2009;3:CD004437*

**Study:** Systematic review of randomized controlled trials comparing thrombolytic therapy with placebo, heparin, or surgical intervention.

**Patients:** 679 patients with acute PE.

**Intervention:** Thrombolytics vs. heparin or placebo.

**Outcome:** Death rate, recurrence of PE, major and minor hemorrhagic events.

**Results:** Non-significant difference between thrombolytics and heparin or placebo in all measured outcomes. Rt-PA and heparin together reduced need for treatment for in-hospital events. Thrombolytics improved hemodynamic outcome, lung VQ scans, pulmonary angio assessment and echocardiograms greater than heparin. Need for further double-blinded RCTs.

**Conclusion:** We cannot conclude whether thrombolytic therapy is better than heparin for pulmonary embolism based on limited evidence found.

- vascular stents may help improve long term results by keeping the vessel wall patent after PTA
- stents are also used for angioplasty failure or complications
- stent grafts (metal mesh covered with durable fabric) may provide an alternative treatment option for aneurysms and AV fistulas
- complications: similar to angiography, but also includes vessel rupture

### Thrombolytic Therapy

- may be systemic (IV) or catheter directed
- infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
- can restore blood flow in a vessel obstructed with a thrombus or embolus
- indications: treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of venous thrombosis (DVT or PE)
- complications: bleeding, stroke, distal embolus, reperfusion injury with myoglobinuria and renal failure if advanced ischemia present

### Embolization

- injection of occluding material into vessels
- permanent agents: amplatzer plugs, coils, glue and onyx
- temporary: gel foam, autologous blood clots
- indications: management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of AVM, pre-operative treatment of vascular tumours (bone metastases, renal cell carcinoma), varicocele embolization for infertility, symptomatic uterine fibroids
- complications
  - post embolization syndrome (pain, fever, leukocytosis)
  - unintentional embolization of a non-target organ with resultant ischemia

### Inferior Vena Cava Filter

- insertion of metallic “umbrellas” to mechanically trap emboli and prevent PE
- may be temporary (retrievable) or permanent
- inserted via femoral vein, jugular vein, or antecubital vein
- usually placed infrarenally to avoid renal vein thrombosis
- indications: contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation

### Central Venous Access

- variety of devices available
- peripherally inserted central catheter (PICC), external tunneled catheter (Hickman or dialysis catheters), subcutaneous port (Portacath®)
- indications: chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
- complications: venous thrombosis and central venous stenosis, infection including sepsis, pneumothorax



Advanced ischemia patients should receive surgery rather than thrombolysis.



Chemoembolization delivers chemotherapy directly into the tumour through its feeding blood supply and traps the drug in place by embolization.



#### Indications for Central Venous Access

##### FAT CAB

Fluids  
Antibiotics  
TPN  
Chemotherapy  
Administration of blood  
Blood sampling



Figure 36. Retrievable IVC filter



Figure 37. Femoral arteriogram: distal occlusion of superficial femoral artery



ERCP is the primary modality for distal common bile duct obstructions.

## Nonvascular Interventions

### Percutaneous Biopsy

- replaces open surgical procedure
- many sites are amenable to biopsy using U/S, fluoroscopy or CT guidance
- complications:
  - false negative biopsies due to sampling error or tissue necrosis
  - pneumothorax in 30% of lung biopsies, chest tube required in approximately 5%
  - pancreatic biopsies are associated with risk of inducing acute pancreatitis
  - transjugular liver biopsies can be performed to minimize bleeding complications in patients with uncorrectable coagulopathies or ascites

### Abscess Drainage

- placement of a drainage catheter into an infected fluid collection
- administer broad spectrum IV antibiotics prior to procedure
- routes: percutaneous (most common), transgluteal, transvaginal, transrectal
- complications:
  - hemorrhage
  - injury to intervening structures (e.g. bowel)
  - bacteremia, sepsis

**Percutaneous Biliary Drainage (PBD)/Cholecystostomy**

- placement of drainage catheter ± metallic stent into obstructed biliary system (PBD) or gallbladder (cholecystostomy) for relief of jaundice or infection
- percutaneous gallbladder access can be used to crush or remove stones
- indications:
  - cholecystitis: acute cholecystitis
  - percutaneous biliary drainage: biliary obstruction secondary to stone or tumour, cholangitis
- complications:
  - acute: sepsis, hemorrhage
  - long-term: tumour overgrowth and stent occlusion

**Percutaneous Nephrostomy**

- placement of catheter into renal collecting system
- indications: hydronephrosis (urinary obstruction as a result of a stone or tumour), pyonephrosis, ureteric injury with or without urinary peritonitis (traumatic or iatrogenic)
- complications: bacteria and septic shock, hematuria due to pseudoaneurysm or AV fistulas, injury to adjacent organs

**Gastrostomy/Gastrojejunostomy**

- percutaneous placement of catheter directly into either stomach (gastrostomy) or through stomach into small bowel (transgastric jejunostomy)
- indications:
  - feeding: inability to eat (most commonly CNS lesion, e.g. stroke) or esophageal obstruction
  - decompression: gastric outlet obstruction
- complications: gastroesophageal reflux with aspiration, peritonitis, hemorrhage, bowel or solid organ injury

**Radiofrequency (RF) Ablation**

- U/S or CT guided probe is inserted into tumour, RF energy delivered through probe causes heat deposition and tissue destruction
- indications: hepatic tumours (HCC and metastases), renal tumours
- complications: destruction of neighbouring tissues and structures, bleeding

## Breast Imaging

### Modalities

**Mammography****Description**

- x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities (see [General Surgery](#), GS54)

**Indications**

- screening
  - begin screening from age 50 q1-2 yr
  - if over the age of 70, continue screening mammography if in good general health
  - not routinely recommended if under the age of 50 unless strong family history
  - if positive family Hx, begin screening 5-10 yr younger than the first degree relative who developed breast cancer
- diagnostic
  - signs and symptoms suggestive of breast cancer include a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, and spontaneous serous or sanguinous nipple discharge from a single duct
  - women with abnormal screening mammograms
  - follow-up of women with previous breast cancer
  - suspected complications of breast implants

**Table 20. Breast Imaging Reporting and Data System (BI-RADS®) Mammography Categories**

Assessment Categories	Imaging Findings	Follow-up Recommendations
BI-RADS 0	Incomplete	Additional imaging Comparison to prior films
BI-RADS 1	Negative	Routine screening
BI-RADS 2	Benign	Routine screening
BI-RADS 3	Probably benign Likelihood of malignancy is <2%	Unilateral mammogram at 6 mo
BI-RADS 4	Suspicious abnormality	Biopsy
BI-RADS 5	Highly suspicious of malignancy Likelihood of malignancy is 95%	Biopsy
BI-RADS 6	Malignancy confirmed by biopsy	Definitive therapy

## Breast MRI

### Description

- breast MRI should be used only after mammography and ultrasound investigation
- sensitive for detecting invasive breast cancer (95-100%) but specificity variable (37-97%)
- use as a screening modality has been limited to high risk patients

### Indications

- evaluation of previously diagnosed breast cancer: positive margins, recurrence, response to chemotherapy
- post-surgical resection of breast cancer
- known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer
- untested first-degree relative of a carrier of such a gene mutation
- family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%
- high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ)
- radiation therapy to chest (before age 30)
- NOTE: MRI should not be used to screen the general population or to differentiate between benign and malignant lesions

## Ultrasound

### Definition

- ultrasound can determine if a mass is cystic or solid and is commonly used during biopsy

### Indications

- identification and characterization of palpable abnormalities
- evaluation of ambiguous mammographic findings in the determination of cystic versus solid characteristics
- evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
- guidance for interventional procedures
- breast sonography is the initial imaging technique to evaluate palpable masses in women under 30 and in lactating and pregnant women

## Breast Interventional Procedures

### Description

- breast interventional procedures include fine needle aspirate biopsy, core needle biopsy, abscess drainage, and cyst aspiration (see [General Surgery](#), GS56)



### Indications

- cystic mass: complex cyst, symptomatic, suspected abscess
- solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) or confirm diagnosis of a probable benign mass (BI-RADS® Category 3)
- initial percutaneous biopsy procedure that was insufficient or discordant with imaging
- presurgical ultrasound-guided localization of a lesion

## Breast Findings

### Breast Masses

- definition: a space occupying lesion seen in two different projections; if seen in only a single projection it should be called a “density” until its three-dimensionality is confirmed

**Table 21. Mammographic Features of Benign and Malignant Breast Masses**

	Benign	Malignant
<b>Shape</b>	Oval, round, lobular	Irregular
<b>Margin</b>	Circumscribed, well-defined	Indistinct, microlobulated, speculated
<b>Density</b>	Radiolucent (oil cyst, lipoma, fibrolipoma, galactocoele, hamartoma)	Radiodense
<b>Calcifications (± mass)</b>	Popcorn (hyalinizing fibroadenoma), lucent centred (oil cyst/fat necrosis), layering (milk of calcium), vascular, round, scattered	Pleomorphic (vary in size and shape), amorphous (indistinct), fine linear, coarse heterogenous, regional, segmental, clustered

### Other Findings

- tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
- intramammary lymph node: typical lymph nodes are circumscribed, reniform and often have a fatty notch and centre; usually less than 1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty centre or notch) are well seen, the lesion is almost always benign and insignificant
- focal asymmetric density: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
  - if focal compression shows mass-like character, or if the area can be palpated, biopsy must be considered

## References

- American College of Radiology (ACR) breast imaging reporting and data system atlas (BI-RADS atlas). Reston: American College of Radiology, 2003.
- Brant WE, Helms CA. Fundamentals of diagnostic radiology. Philadelphia: Lippincott Williams and Wilkins, 1999.
- Canadian Association of Radiologists (CAR) standard for breast Imaging. Ottawa: Canadian Association of Radiologists, 1998.
- Canadian Association of Radiologists (CAR) standard for performance of breast ultrasound examination. Ottawa: Canadian Association of Radiologists, 2003.
- Canadian Association of Radiologists (CAR) standards for the performance of ultrasound-guided percutaneous breast interventional procedures. Ottawa: Canadian Association of Radiologists, 2003.
- Chen MYM, Pope TL, Ott DJ. Basic radiology. New York: Lange Medical Books/McGraw Hill, 2004.
- Daffner RH. Clinical radiology: the essentials. Baltimore: Williams & Wilkins, 1993.
- Erkonen WE, Smith WL. Radiology 101. Philadelphia: Lippincott Williams & Wilkins, 2005.
- Fleckenstein P, Tranun-Jensen J. Anatomy in diagnostic imaging, 2nd ed. Copenhagen: Blackwell Publishing, 2001.
- Gay S, Woodcock Jr RJ. Radiology recall. Baltimore: Lippincott Williams & Wilkins, 2000.
- Goldstein S. Saline infusion sonohysterogram. Up to Date, 2012.
- Goodman LR. Felson's principles of chest roentgenology: a programmed text, 3rd ed. Philadelphia: Saunders, 2007.
- Joffe SA, et al. Multi-detector row CT urography in the evaluation of hematuria. Radiographics 2003;23:1441-1455.
- Juhl JH, Crummy AB, Kuhlman JE. Paul and Juhl's essentials of radiologic imaging. Philadelphia: Lippincott-Raven, 1998.
- Katz DS, Math KR, Groskin SA. Radiology secrets. Philadelphia: Hanley and Belfus, 1998.
- Mettler FA Jr, et al. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology 2008;248:254-263.
- Novelline RA. Squire's fundamentals of radiology, 6th ed. Cambridge: Harvard, 2004.
- Ouellette H, Tetreault P. Clinical radiology made ridiculously simple. Miami: MedMaster, 2002.
- Sam PM, Curtin HD. Head and neck imaging, 3rd ed. St. Louis: Mosby, 1996.
- Warner E, et al. Cancer Care Ontario's Program in Evidence-based Care. 2007. Magnetic resonance imaging screening of women at high risk for breast cancer: a clinical practice guideline.
- Weissleder R, Rieumont MJ, Wittenberg J. Primer of diagnostic imaging, 2nd ed. Philadelphia: Mosby, 1997.
- Young WF. Clinical practice. The incidentally discovered adrenal mass. NEJM 2007;356:601-610.

Ryan Luther and Constantin Shuster, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Ramesh Prasad and Dr. Alireza Zahirieh, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Systemic Disease with Renal</b>	
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	<b>Manifestation</b> . . . . .	<b>28</b>
Anatomy of the Kidney		Diabetes	
Renal Structure and Function		Scleroderma	
Renal Hemodynamics		Multiple Myeloma	
		Malignancy	
<b>Assessment of Renal Function</b> . . . . .	<b>4</b>	<b>Hypertension (HTN)</b> . . . . .	<b>30</b>
Measurement of Renal Function		Hypertensive Nephrosclerosis	
Urinalysis		Renovascular Hypertension	
Urine Microscopy		Renal Parenchymal Hypertension	
Urine Electrolytes			
<b>Electrolyte Disorders</b> . . . . .	<b>7</b>	<b>Cystic Diseases of the Kidney</b> . . . . .	<b>31</b>
Sodium Homeostasis		Adult Polycystic Kidney Disease	
Hyponatremia		Medullary Sponge Kidney	
Hypernatremia		Autosomal Recessive Polycystic Kidney Disease	
Potassium Homeostasis			
Hypokalemia		<b>Acute Kidney Injury (AKI)</b> . . . . .	<b>33</b>
Hyperkalemia		Approach to AKI	
<b>Acid-Base Disorders</b> . . . . .	<b>14</b>	<b>Chronic Kidney Disease (CKD)</b> . . . . .	<b>34</b>
Metabolic Acidosis		Management of Chronic Kidney Disease	
Metabolic Alkalosis			
<b>Vascular Diseases of the Kidney</b> . . . . .	<b>17</b>	<b>Renal Failure</b> . . . . .	<b>35</b>
Large Vessel Disease		Presentation of Renal Failure	
Small Vessel Disease			
<b>Glomerular Disease</b> . . . . .	<b>19</b>	<b>Renal Replacement Therapy</b> . . . . .	<b>36</b>
Histological Terms for Glomerular Changes		Dialysis	
Clinical Presentation of Glomerular Disease		Renal Transplantation	
Glomerular Syndromes			
Investigations for Glomerular Disease		<b>Common Medications</b> . . . . .	<b>38</b>
Secondary Causes of Glomerular Disease		<b>Landmark Nephrology Trials</b> . . . . .	<b>39</b>
<b>Tubulointerstitial Disease</b> . . . . .	<b>25</b>	<b>References</b> . . . . .	<b>40</b>
Tubulointerstitial Nephritis (TIN)			
Acute Tubular Necrosis (ATN)			
Analgesic Nephropathies			



## Basic Anatomy Review

### Anatomy of the Kidney

- see [Urology](#), U2



### Renal Structure and Function

#### The Nephron

- basic structural and functional unit of the kidney, approximately 1 million per kidney
- 2 main components: glomerulus and attached renal tubule
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

**Table 1. Major Functions of the Kidneys**

Function	Mechanism	Affected Elements
1. Waste Excretion	Glomerular filtration	Excretion of nitrogenous products of protein metabolism (urea, Cr)
	Tubular secretion	Excretion of organic acids (urate) and organic bases (Cr)
	Tubular catabolism	Breakdown and excretion of drugs (antibiotics, diuretics) and peptide hormones (most pituitary hormones, insulin, glucagon)
2. Electrolyte Balance	Tubular NaCl and water reabsorption	Controls volume status and osmolar balance
	Tubular K <sup>+</sup> secretion	Controls potassium concentration
	Tubular H <sup>+</sup> secretion	Acid-base balance
	HCO <sub>3</sub> <sup>-</sup> synthesis and reabsorption	Acid-base balance
	Tubular Ca <sup>2+</sup> , Mg <sup>2+</sup> , PO <sub>4</sub> <sup>3-</sup> transport	Alters Ca <sup>2+</sup> , Mg <sup>2+</sup> , PO <sub>4</sub> <sup>3-</sup> homeostasis
3. Hormonal Synthesis	Erythropoietin production (cortex)	Red blood cell production
	Vitamin D activation [25(OH) <sub>2</sub> D, 1,25(OH) <sub>2</sub> D]	Calcium homeostasis
	Renin production (JG apparatus)	Alters vascular resistance and aldosterone secretion
4. Blood Pressure Regulation	Na <sup>+</sup> excretion	Alters ECF volume
	Renin production	Alters vascular resistance
5. Glucose Homeostasis	Gluconeogenesis (from lactate, pyruvate and amino acids)	Glucose supply maintained in prolonged starvation

#### The Glomerulus

- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- consists of following cell types:
  1. Mesangial cells
    - structural cells that support the vascular tree. They are also contractile and produce vasoactive substances to help control blood flow
  2. Capillary endothelial cells
    - one of the cells of the glomerular filtration barrier and help form the plasma filtration apparatus due to their sinusoidal nature and glycocalyx. Contribute to the production of the glomerular basement membrane (GBM)
  3. Visceral epithelium (podocytes)
    - one of the cells of the glomerular filtration barrier and help form the plasma filtration apparatus due to their interdigitated foot process that form slit diaphragms. Contribute to the production of the glomerular basement membrane (GBM)
  4. Parietal epithelium
    - lines the interior of Bowman's capsule and contains a podocyte progenitor population
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman's space (Figure 1)
- particles are selectively filtered by size (<60 kDa) and charge (negative charge repelled)

## Acronyms

ACEI	angiotensin converting enzyme inhibitor
ACR	albumin to Cr ratio
ADH	antidiuretic hormone
AG	anion gap
AIN	acute interstitial nephritis
AKI	acute kidney injury
ANA	antinuclear antibody
Anti-GBM	anti-glomerular basement membrane
ARB	angiotensin receptor blocker
ARF	acute renal failure
ASA	acetylsalicylic acid
ATN	acute tubular necrosis
AVM	arteriovenous malformation
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
C&S	culture and sensitivity
CHF	congestive heart failure
Cr	creatinine
CrCl	creatinine clearance
CRF	chronic renal failure
D5W	5% dextrose in water
DDAVP	1-desamino-8-d-arginine vasopressin
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
DM	diabetes mellitus
EGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
GFR	glomerular filtration rate
GN	glomerulonephritis
HCTZ	hydrochlorothiazide
HSP	Henoch-Schönlein Purpura
HTN	hypertension
HUS	hemolytic uremic syndrome
IVP	intravenous pyelogram
LOC	level of consciousness
MDRD	modification of diet in renal disease
NS	normal saline
NSAIDs	nonsteroidal anti-inflammatory drugs
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibody
PCKD	polycystic kidney disease
PTH	parathyroid hormone
R&M	routine and microscopy
RAAS	renin-angiotensin-aldosterone system
RBF	renal blood flow
RCC	renal cell carcinoma
RPGN	rapidly progressive glomerulonephritis
RRT	renal replacement therapy
RTA	renal tubular acidosis
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosus
TIN	tubulointerstitial nephritis
TTP	thrombotic thrombocytopenic purpura
UTI	urinary tract infection

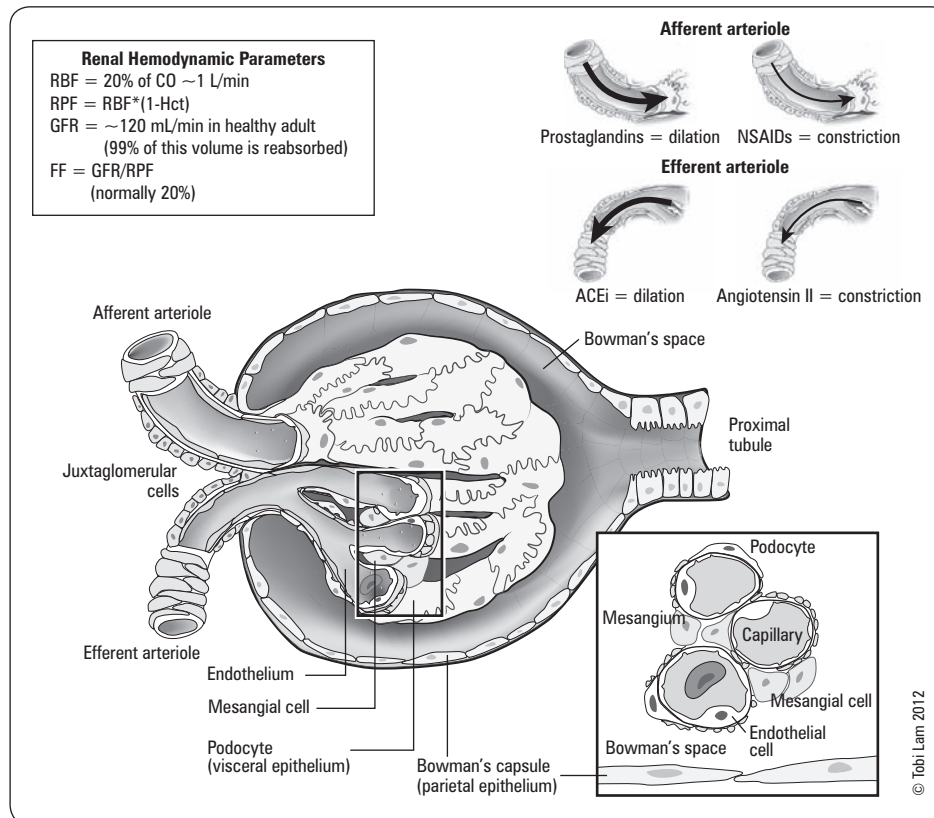


Figure 1. The glomerulus

### The Renal Tubules

- reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion
- each segment of the nephron selectively transports various solutes and water and is targeted by specific diuretics

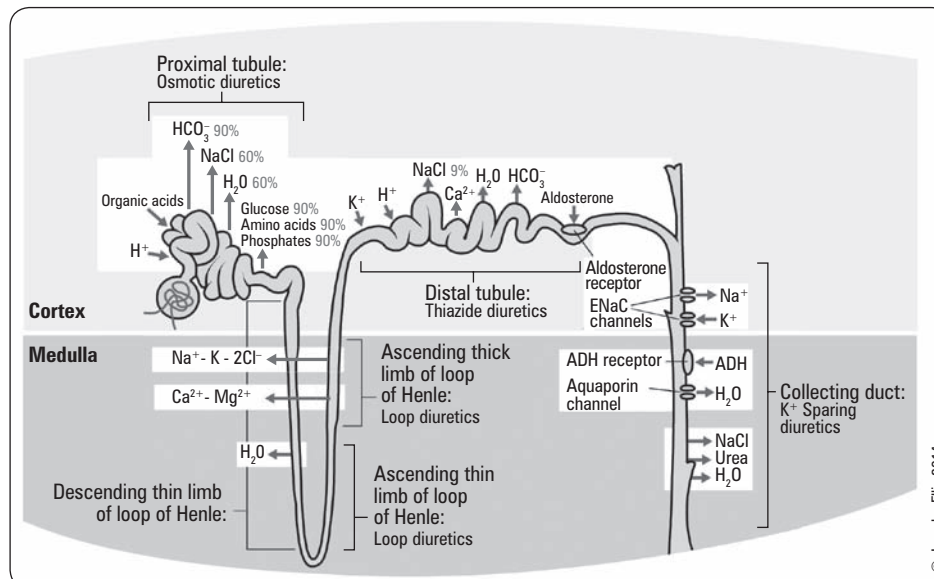


Figure 2. Tubular segments of the nephron

## Renal Hemodynamics

- Glomerular Filtration Rate (GFR)
  - the rate of fluid transfer between glomerular capillaries and Bowman's space
  - 180 L/d, of which 99% is reabsorbed, giving a daily urine output of 1.0-1.5 L
  - normal urine output is >0.5 ml/kg/h in adults
  - GFR is highest in early adulthood, decreasing thereafter
- renal autoregulation maintains constant GFR over mean arterial pressures of 70-180 mmHg
- 2 mechanisms of autoregulation:
  - myogenic mechanism: release of vasoactive factors in response to changes in perfusion pressure (e.g. ↑ perfusion pressure → afferent arteriolar constriction → ↓ GFR)
  - tubuloglomerular feedback: changes in  $[Na^+]$  delivery to macula densa lead to afferent arteriolar tone (e.g. increased delivery causes afferent constriction)
- Filtration Fraction (FF)
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio:  $FF = GFR/RPF$ ; normal = 0.2 or 20%
  - angiotensin II ( $A_{II}$ ) constricts renal efferent arterioles which increases FF thereby maintaining GFR
- renin is released from juxtaglomerular apparatus in response to decreased RPF



### Glomerular Filtration Rate

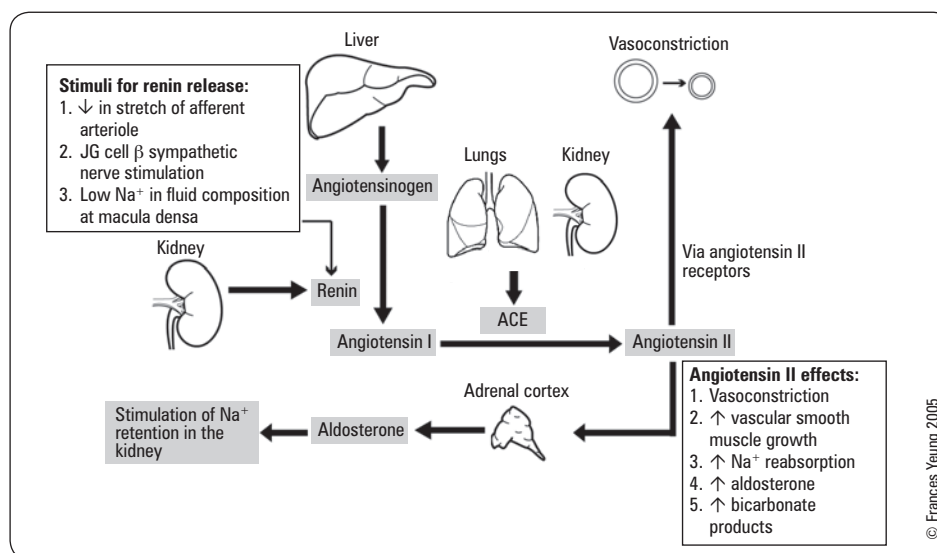
$$GFR = K_f (\Delta P - \Delta \Pi)$$

$K_f$  = ultrafiltration coefficient

$\Delta P$  = hydrostatic pressure difference between glomerular capillaries and Bowman's space

$\Delta \Pi$  = osmotic pressure difference between glomerular capillaries and Bowman's space

$\Delta P - \Delta \Pi$  = Net outward pressure



© Frances Yeung 2005

Figure 3. Stimuli for renin release

## Assessment of Renal Function

### Measurement of Renal Function

- glomerular filtration rate (GFR) = rate of filtration of plasma by the glomeruli
- most renal functions decline in parallel with a decrease in GFR
- inulin clearance is the gold standard for measuring GFR, but very rarely used clinically
- clinically, GFR is estimated using serum creatinine concentrations  $[Cr]$
- creatinine (Cr) is a metabolite of creatine (intermediate in muscle energy metabolism)
- Cr is freely filtered at the glomerulus with no tubular reabsorption
- tubular secretion varies based on level of renal function (10% to >50%)
- rate of production determined by muscle mass
- Cr filtered  $\approx$  Cr excreted (at steady state)

### Ways to Estimate GFR Using Serum Creatinine Concentration

1. Calculate creatinine clearance (CrCl)
  - calculation provides reasonable estimate of GFR
  - measure plasma  $[Cr]$ , 24-h urine volume and urine  $[Cr]$ 
    - $GFR/d = (urine [Cr] \times urine volume/d) / (plasma [Cr])$
    - must use same units for urine  $[Cr]$  and plasma  $[Cr]$
2. Cockcroft-Gault formula
  - serum Cr used along with age, gender and weight (kg) to estimate GFR (see sidebar)
  - normal range is >90 mL/min (>1.5 mL/s)



$$Cr_{filtered} = Cr_{excreted}$$

$$[Cr]_{plasma} \times GFR = [Cr]_{urine} \times \text{urine flow rate (mL/min)}$$

$$GFR = \frac{[Cr]_{urine} \times \text{urine flow rate}}{[Cr]_{plasma}}$$



At steady state  $[Cr]_{serum} \propto 1/CrCl$



### Cockcroft-Gault Formula

$$CrCl \text{ (mL/min)} = \frac{(\text{weight in kg}) (140 - \text{age}) \times 1.23}{\text{serum creatinine (umol/L)}}$$

Multiply above by 0.85 for females.

**3. MDRD (Modification of Diet in Renal Disease) formula**

- most common way in which GFR is estimated (MDRD 7 equation)
- complex formula incorporating age, gender, serum Cr, African descent, but does not include weight
- GFR is reported as mL/min/1.73 m<sup>2</sup> body surface area

**4. CKD-EPI equation**

- the best current equation
- calculated using serum Cr, age, sex and race

**Limitations of Using Serum Cr Measurements**

1. must be in steady state
  - constant GFR and rate of production of Cr from muscles
  - sudden injury may reduce GFR substantially, but it takes time for Cr to accumulate and then re-establish steady state
  - clinical correlation: in acute kidney injury, the rise in creatinine is often delayed
2. GFR must fall substantially before plasma [Cr] rises above normal laboratory range
  - with progressive renal failure, remaining nephrons compensate with hyperfiltration
  - GFR is relatively preserved despite significant structural damage
3. plasma [Cr] is influenced by the rate of Cr production
  - lower production with smaller muscle mass (i.e. female, elderly, low weight)
  - e.g. consider plasma [Cr] of 100 µmol/L (1.13 mg/dL) in both of these patients
    - ♦ 20 yr-old man who weighs 100 kg, GFR = 144 mL/min
    - ♦ 80 yr-old woman who weighs 50 kg, GFR = 30.6 mL/min
  - clinical correlation: GFR decreases with age but would not be reflected as a rise in serum creatinine due to the age-associated decline in muscle mass
4. tubular secretion of creatinine increases as GFR decreases
  - serum creatinine and CrCl overestimate low GFR
  - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
5. errors in Cr measurement
  - very high bilirubin level causes [Cr] to be falsely low
  - acetoacetate (a ketone body) and certain drugs (cefexitin) create falsely high [Cr]

**Measurement of Urea Concentration**

- urea is the major end product of protein metabolism
- plasma urea concentration reflects renal function but should not be used alone as it is modified by a variety of other factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) cause urea level to rise
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in sodium-avid states such as ECF volume depletion
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mmol/L for urea and µmol/L for Cr), and 14:1 in MKS units (urea expressed as BUN in mg/dL and Cr in mg/dL)

**Cystatin C**

Cystatin C is a protease which is completely filtered by the glomerulus and is not affected by muscle mass. It is not currently used in clinical practice but may be a more accurate way to measure renal function in the future, particularly in diabetes.

**Clinical Settings in which Urea Level is Affected Independent of Renal Function****Disproportionate Increase in Urea**

- Volume depletion (prerenal azotemia)
- GI hemorrhage
- High protein diet
- Sepsis
- Catabolic state with tissue breakdown
- Corticosteroid or cytotoxic agents

**Disproportionate Decrease in Urea**

- Low protein diet
- Liver disease

## Urinalysis

- use dipstick in freshly voided urine specimen to assess the following:

**1. Specific Gravity**

- ratio of the mass of equal volumes of urine/H<sub>2</sub>O
- range is 1.001 to 1.030
- values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
- value usually 1.010 in end stage renal disease (isosthenuria)

**2. pH**

- urine pH is normally between 4.5-7.0; if persistently alkaline, consider:
  - renal tubular acidosis
  - UTI with urease-producing bacteria (e.g. *Proteus*)

**3. Glucose**

- freely filtered at glomerulus and reabsorbed in proximal tubule
- causes of glucosuria include
  1. hyperglycemia >9-11 mmol/L (>160-200 mg/dL) leads to filtration that exceeds tubular resorption capacity
  2. increased GFR (e.g. pregnancy)
  3. proximal tubule dysfunction (e.g. Fanconi's syndrome)

**4. Protein**

- dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
- microalbuminuria (defined as ≥2.0 mg/mmol creatinine in males and ≥2.8 mg/mmol creatinine in females) is not detected by standard dipstick (see *Diabetes and the Kidney*, NP28)
- sulfosalicylic acid detects all protein in urine by precipitation
- gold standard: 24-h timed urine collection for total protein

**24 h Urine Collection**

- Discard first morning specimen
- Collect all subsequent urine for the next 24 h
- Refrigerate between voids
- Collect second morning specimen

**Clarity:** Cloudiness may indicate infection

**Colour:** usually pale yellow or amber, but may be colourless (diabetes insipidus, excess water intake), bright yellow (due to riboflavin ingestion or vitamin tablets), or dark yellow (concentrated urine in intravascular volume depletion)

**Estimating Urine Osmolality**

Last 2 digits of the specific gravity x 30  
= urine osmolality approximately  
e.g. specific gravity of 1.020  
= 600 mOsm

### 5. Leukocyte Esterase

- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation (e.g. AIN)

### 6. Nitrites

- nitrates in urine are converted by bacteria to nitrites
- high specificity, low sensitivity for UTI

### 7. Ketones

- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

### 8. Hemoglobin

- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis) and true hematuria (RBCs seen on microscopy)

## Urine Microscopy

- centrifuge urine specimen for 3-5 min, discard supernatant, resuspend sediment and plate on slide
- shaking tube vigorously may disrupt casts

**Table 2. Comparison of Urinary Sediment Findings**

	Active Sediment	Bland Sediment
<b>Any one or more of the following seen on microscopy</b>	Red cell casts White cell casts Muddy-brown granular or epithelial cell casts >2 red cells per high power field (HPF) >4 white cells per HPF	Only hyaline casts <2 red cells per HPF <4 white cells per HPF Small quantities of crystals Small amount of bacteria
<b>Significance</b>	Highly suggestive of significant pathology, casts specifically suggest renal pathology	Reduced likelihood of significant pathology, but not ruled out

### 1. CELLS

#### Erythrocytes

- normal range = up to 2-3 RBCs per high power field (HPF)
- hematuria = greater than 2-3 RBCs/HPF
- dysmorphic RBCs and/or RBC casts suggest glomerular bleeding (e.g. proliferative glomerulonephritis)
- isomorphic RBCs, no casts suggest extraglomerular bleeding (e.g. bladder Ca)

#### Leukocytes

- normal range = up to 3 WBCs/HPF
- pyuria = greater than 3 WBCs/HPF
- indicates inflammation or infection
- if persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, papillary necrosis, renal TB, viral infections

#### Eosinophils

- detected using Wright's or Hansel's stain (not affected by urine pH)
- consider allergic interstitial nephritis, atheroembolic disease

#### Oval Fat Bodies

- renal tubular cells filled with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

### 3. CASTS

- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein

**Table 3. Interpretation of Casts**

Hyaline casts	Physiologic (concentrated urine, fever, exercise)
Red blood cell casts	Glomerular bleeding (glomerulonephritis, vasculitis)
White blood cell casts	Infection (pyelonephritis) Inflammation (interstitial nephritis)
Pigmented granular casts (heme granular casts, muddy brown)	Acute tubular necrosis Acute glomerulonephritis
Fatty casts	Heavy proteinuria (>3.5 g/d)



Positive dipstick for leukocyte esterase and nitrites is 94% specific for diagnosing a UTI.



### 3. CRYSTALS

- uric acid: consider acid urine, hyperuricosuria
- calcium phosphate: alkaline urine
- calcium oxalate: consider hyperoxaluria, ethylene glycol poisoning
- sulfur: sulfa-containing antibiotics

## Urine Electrolytes

- commonly measure:  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$ , osmolality and pH
- no 'normal' values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient's current state, e.g.:
  1. ECF volume depletion: expect low urine  $[\text{Na}^+]$  (kidneys should be retaining  $\text{Na}^+$ )
    - ♦ urine  $[\text{Na}^+] > 40 \text{ mmol/L}$  suggests a renal problem or the action of a diuretic
    - ♦ urine  $[\text{Na}^+] < 20 \text{ mmol/L}$  suggests the patient is pre-renal
  2. daily urinary potassium excretion rate should be decreased ( $< 20 \text{ mmol/d}$ ) in hypokalemia
    - ♦ if higher than  $20 \text{ mmol/d}$ , suggests renal contribution to hypokalemia
- osmolality is useful to estimate the kidney's concentrating ability
- $\text{FE}_{\text{Na}}$  refers to the fractional excretion of  $\text{Na}^+$ 
  - $\text{FE}_{\text{Na}} = \frac{\text{Urine } [\text{Na}^+] \times \text{Plasma } [\text{Cr}]}{\text{Plasma } [\text{Na}^+] \times \text{Urine } [\text{Cr}]}$
  - $\text{FE}_{\text{Na}} < 1\%$  suggests the pathology is pre-renal

### Examples of Common Urine Electrolyte Abnormalities

- high urine  $[\text{Na}^+] (> 40 \text{ mmol/L})$  in the setting of acute renal failure: indicates renal disease
- high urine  $[\text{Na}^+] (> 40 \text{ mmol/L})$  in the setting of hyponatremia: generally from causes such as diuretics, tubular disease (e.g. Bartter's syndrome), SIADH
- additionally, urine pH is useful to grossly assess renal acidification
- "low" pH ( $< 5.5$ ) in the presence of low serum pH is an appropriate renal response
- a high pH in this setting might indicate a renal acidification defect (e.g. RTA)



#### Fractional Excretion of Sodium

$$\text{FE}_{\text{Na}} = \frac{[\text{Na}^+]_{\text{Urine}} \times [\text{Cr}]_{\text{Plasma}}}{[\text{Na}^+]_{\text{Plasma}} \times [\text{Cr}]_{\text{Urine}}} \times 100$$

Many formulas used in nephrology are derived from the division of two fractions, each of which compare a urine and plasma concentration (e.g.  $\text{U}_1/\text{P}_1 \div \text{U}_2/\text{P}_2$ ). In the case of  $\text{FE}_{\text{Na}}$ , it is  $\text{U}_{\text{Na}}/\text{P}_{\text{Na}} \div \text{U}_{\text{Cr}}/\text{P}_{\text{Cr}}$ , which then gives the above equation.

## Electrolyte Disorders

### Sodium Homeostasis

- hyponatremia and hypernatremia are disorders of water balance
  - hyponatremia usually suggests too much water in the extracellular fluid relative to  $\text{Na}^+$
  - hypernatremia usually suggests too little water in the extracellular fluid relative to  $\text{Na}^+$
- solutes (such as  $\text{Na}^+$ ,  $\text{K}^+$ , glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
  - water moves out of cells in response to increased ECF osmolality
  - water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by  $\text{Na}^+$  content rather than concentration
  - $\text{Na}^+$  deficiency leads to ECF volume contraction
  - $\text{Na}^+$  excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially in the brain) shrinking (hypernatremia) or swelling (hyponatremia)



#### Common Electrolytes

- Sodium ( $\text{Na}^+$ ) 135-145 mmol/L
- Potassium ( $\text{K}^+$ ) 3.5-5 mmol/L
- Chloride ( $\text{Cl}^-$ ) 95-105 mmol/L
- Bicarbonate ( $\text{HCO}_3^-$ ) 18-23 mmol/L

**Table 4. Clinical Assessment of ECF Volume (Total Body  $\text{Na}^+$ )**

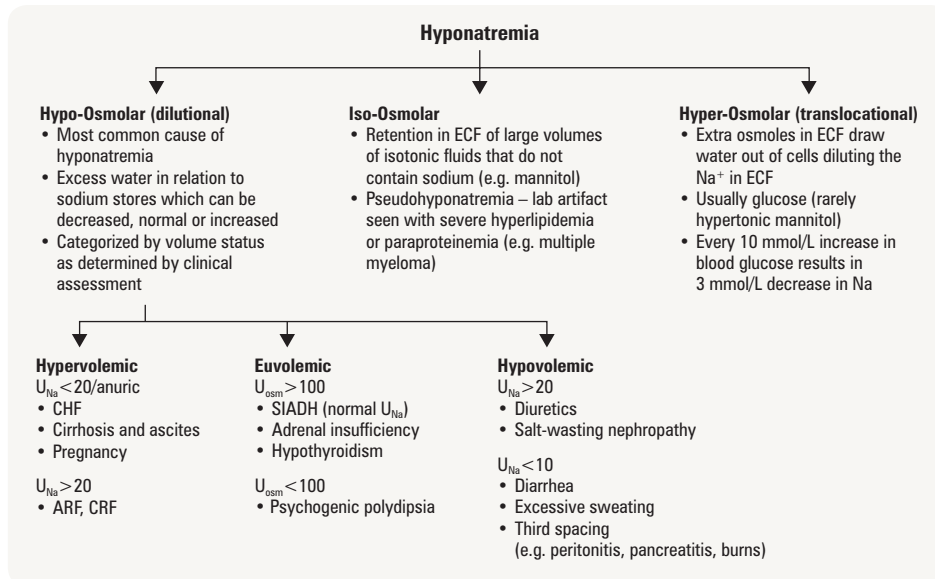
Fluid Compartment	Hypovolemic	Hypervolemic
<b>Intravascular</b>		
JVP	Decreased	Increased
Blood pressure	Orthostatic drop	Normal to increased
Auscultation of heart	Tachycardia	S3
Auscultation of lungs	Normal	Inspiratory crackles
<b>Interstitial</b>		
Skin turgor	Decreased	Normal/increased
Edema (dependent)	Absent	Present
<b>Other</b>		
Urine output	Decreased*	Variable
Body weight	Decreased	Increased
Hct, serum protein	Increased	Decreased

\*If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia



## Hyponatremia

- hyponatremia: serum  $[\text{Na}^+]$   $<136$  mmol/L
- can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality



If the urine osmolality is unknown, assume the urine is hypo-osmolar/dilute.

Figure 4. Approach to hyponatremia

### Signs and Symptoms

- depend on degree of hyponatremia and more importantly, velocity of progression from onset
- acute hyponatremia ( $<24$ -48 h) more likely to be symptomatic
- chronic hyponatremia ( $>24$ -48 h) less likely to be symptomatic due to adaptation
  - adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days)
  - adaptation is responsible for the risks associated with overly rapid correction
- neurologic symptoms predominate (secondary to cerebral edema): headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased level of consciousness (LOC)

### Complications

- seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death
- risk of brain cell shrinkage with rapid correction of hyponatremia
  - can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible (e.g. central pontine myelinolysis: cranial nerve palsies, quadriplegia, decreased LOC)

### Risk Factors for Osmotic Demyelination

- rise in serum  $[\text{Na}^+]$  with correction  $>8$  mmol/L/d if chronic hyponatremia
- associated hypokalemia and/or malnutrition (i.e. low muscle mass)
- if patient with hyponatremia and hypovolemia is given large volume of isotonic fluid (ADH is stimulated by hypovolemia; when hypovolemia is corrected, the ADH level falls suddenly causing sudden brisk water diuresis, and therefore rapid rise in serum  $\text{Na}^+$  level)
- patient with psychogenic polydipsia, deprived of water

### Investigations

- ECF volume status assessment
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine  $\text{Na}^+$  (urine  $\text{Na}^+ <10$ -20 mmol/L suggests volume depletion as the cause of hyponatremia)
- assess for causes of SIADH (see Table 6)
- TSH, free T4, and cortisol levels
- consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. small cell lung Ca)
- consider CT head if suspect CNS cause



**Central Pontine Myelinolysis**

- CN palsies
- Quadriplegia
- Decreased LOC

### Treatment of Hyponatremia

- general measures for all patients
  - water restriction to <1 L/d (unless hypovolemic give normal saline)
  - treat underlying cause
  - monitor serum  $\text{Na}^+$  frequently to ensure correction is not occurring too rapidly
  - monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia

**Table 5. Treatment of Acute and Chronic Hypoosmolar Hyponatremia**

Onset	Symptomatic	Treatment
Acute (<48 h)	Yes	Rapid correction (Hypertonic 3% saline)
	No	Rapid correction only if marked drop in $\text{Na}^+$
Chronic (>48 h)	Yes	Slow correction (Hypertonic 3% saline)
	No	Water restriction, NS, NaCl tablet

#### A. Definitely Acute (known to have developed over <24-48 h)

- commonly occurs in hospital (dilute IV fluid, post-operative increased ADH)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
  - correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum  $[\text{Na}^+] = 125-130 \text{ mmol/L}$
  - may need furosemide to address volume overload
- if asymptomatic, treatment depends on severity
  - if marked fall in plasma  $[\text{Na}^+]$ , treat as symptomatic

#### B. Chronic or Unknown

1. if severe symptoms (seizures or decreased LOC)
  - must partially correct acutely
  - aim for increase of  $\text{Na}^+$  by 1-2 mmol/L/h for 4-6 h
  - limit total rise to 8 mmol/L in 24 h
  - IV 3% NaCl at 1-2 cc/kg/h
  - may need furosemide
2. if asymptomatic
  - water restrict to <1 L/d fluid intake
  - consider IV 0.9% normal saline (NS) + furosemide (reduces urine osmolality, augments excretion of  $\text{H}_2\text{O}$ )
  - consider NaCl tablet or Oxocubes® as a source of  $\text{Na}^+$
3. refractory
  - furosemide and IV NS
  - demeclocycline 300-600 mg PO bid (antagonizes effect of ADH on collecting duct; avoid if cirrhosis or congestive heart failure as nephrotoxic in these settings)
  - extra osmoles – give oral urea (increases loss of water without  $\text{Na}^+$ ; 30-60 g/d)
  - slow rate of IV 3% NaCl (e.g. 10 cc/h = 120 mmol/d of sodium which will increase serum  $[\text{Na}^+]$  by about 3 mmol/L/d)
4. always pay attention to patient's ECF volume status – if already volume-expanded, unlikely to give NaCl; if already volume-depleted, almost never appropriate to give furosemide

#### C. Options if overly rapid correction occurs

- give water (IV D5W)
- give ADH to stop water diuresis (DDAVP 1-2 µg IV)

#### Impact of IV Solution on Plasma $\text{Na}^+$

- formula to estimate the change in serum  $\text{Na}^+$  caused by retention of 1 L of any infusate  
 $[\text{TBW} = (\text{for men}) 0.6 \times \text{wt(kg)}; (\text{for women}) 0.5 \times \text{wt(kg)}]$

$$\text{change in serum } [\text{Na}^+] = \frac{\text{infusate } [\text{Na}^+] - \text{serum } [\text{Na}^+]}{\text{TBW} + 1 \text{ L}}$$

- formula assumes there are no losses of water or electrolytes

### SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

1. urine that is inappropriately concentrated for the serum osmolality
2. high urine sodium (>20-40 mmol/L)
3. high  $\text{FE}_{\text{Na}}$



#### Beware of Rapid Correction of Hyponatremia

- Inadvertent rapid correction of hyponatremia can easily occur
  - e.g. patient with hyponatremia due to SIADH from nausea
  - Anti-emetic given for relief of hyponatremia-induced nausea
  - ADH quickly turned off in the absence of nausea, the kidneys rapidly excrete the excess free water, and the serum  $[\text{Na}^+]$  rises rapidly
- Patient at risk of osmotic demyelination
- High output dilute urine (>100 cc/h, <100 mOsm/L) in the setting of hyponatremia is usually the first sign of dangerously rapid correction of serum sodium



Correction of  $\text{Na}^+$  in hyponatremia should not exceed 8 mmol/L/24 h unless definitely known to be <24-48 h duration. Frequent monitoring of serum  $\text{Na}^+$  and urine output is essential.



#### Concentration of $\text{Na}^+$ in Common Infusates

- $\text{Na}^+$  in 0.45% NaCl = 77 mmol/L
- $\text{Na}^+$  in 0.9% NaCl = 154 mmol/L
- $\text{Na}^+$  in 3% NaCl = 513 mmol/L
- $\text{Na}^+$  in 5% NaCl = 855 mmol/L
- $\text{Na}^+$  in Ringer's lactate = 130 mmol/L
- $\text{Na}^+$  in D5W = 0

**Table 6. Disorders Associated with SIADH**

Tumour	Pulmonary	CNS	Drugs	Miscellaneous
Small cell Ca Bronchogenic Ca Pancreatic AdenoCa Hodgkin's disease Thymoma	Pneumonia Lung abscess TB Acute respiratory failure Positive pressure ventilation	Mass lesion Encephalitis Subarachnoid hemorrhage Stroke Head trauma Acute psychosis Acute intermittent porphyria	<b>Antidepressants</b> TCAs SSRIs <b>Antineoplastics</b> Vincristine Cyclophosphamide <b>Other</b> DDAVP Oxytocin Nicotine Carbamazepine Barbiturates Chlorpropamide ACE inhibitors	Post-op state Pain Severe nausea HIV

## Hypernatremia

- hypernatremia: serum  $[Na^+] > 145$  mmol/L
- too little water relative to total body  $Na^+$ ; always a hyperosmolar state
- usually due to net water loss, rarely due to hypertonic  $Na^+$  gain
- results from problems with water intake (access, thirst) and/or site of increased water loss (renal or extrarenal)
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

### Signs and Symptoms

- with acute hypernatremia no time for adaptation, therefore more likely to be symptomatic
- adaptive response: cells import and generate new osmotically active particles to normalize size
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- $\pm$  polyuria, thirst, signs of hypovolemia

### Complications

- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema due to ongoing brain hyperosmolarity

**Table 7. Treatment Hypovolemic and Hypervolemic Hypernatremia**

Volume Status	Treatment
Hypovolemic	Give free water PO or by NG tube Give IV D5W, 0.45%NS, or 3.3% dextrose with 0.3% NaCl ("2/3 and 1/3")
Hypervolemic	Diuresis or dialysis (D5W once fluid deficit)

### Treatment of Hypovolemic Hypernatremia

- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum  $Na^+$  frequently to ensure correction is not occurring too rapidly
- if evidence of hemodynamic instability, must first correct volume depletion with NS bolus
- loss of water is often accompanied by loss of  $Na^+$  but a proportionately larger water loss
- in patients with presumed normal total body  $Na^+$  content, use formula to calculate  $H_2O$  deficit (see sidebar)
- replace free water deficit
- encourage patient to drink pure water, as oral route is preferred for fluid administration
- if unable to replace PO or NG, correct  $H_2O$  deficit with hypotonic IV solution
- use formula (see *Hyponatremia*, NP9) to estimate expected change in serum  $Na^+$  with 1L infusate
- aim to lower  $[Na^+]$  by no more than 12 mmol/L in 24 h (0.5 mmol/L/h)
- must also provide maintenance fluids and replace ongoing losses
- rule of thumb: give 2 cc/kg/h of free water to correct serum  $[Na^+]$  by about 0.5 mmol/L/h or 12 mmol/L/d

### Treatment of Hypervolemic Hypernatremia

- general measures as above
- hypervolemic hypernatremia: remove excess total body  $Na^+$  with diuresis or dialysis (if renal failure present), then replace water deficit using D5W



#### **$H_2O$ Deficit and TBW Equations**

- TBW =  $0.6 \times \text{wt (kg) men}$ ;  
TBW =  $0.5 \times \text{wt (kg) women}$
- $H_2O$  deficit =  $TBW \times ([Na^+]_{\text{plasma}} - 140) / 140$



Correction of serum  $[Na^+]$  in hypernatremia should not exceed 12 mmol/L/24 h.



1 L D5W approximately equals 1 L of free water  
1 L 0.45% NS approximately equals 500 mL of free water

**DIABETES INSIPIDUS (DI)**

- collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
- central defect in release of ADH (central DI) or renal response to ADH (nephrogenic DI)

**Etiology**

- central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
- nephrogenic DI: lithium (most common), hypokalemia, hypercalcemia, and congenital

**Diagnosis**

- urine osmolality inappropriately low in patient with hypernatremia ( $U_{\text{osm}} < 300 \text{ mOsm/kg}$ )
- serum vasopressin concentration may be absent or low (central), or elevated (nephrogenic)
- dehydration test:  $\text{H}_2\text{O}$  deprivation until loss of 3% of body weight or until urine osmolality rises above plasma osmolality; if fails to concentrate urine, most likely DI
- administer DDAVP (exogenous ADH) ( $10 \mu\text{g}$  intranasally or  $2 \mu\text{g}$  SC or IV):
  - central DI: diagnosed if there is rise in urine osmolality, fall in urine volume
    - treat with DDAVP
  - nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
    - treat with water (IV D5W or PO water), thiazides may help as well (reduced ECF volume stimulates proximal tubular reabsorption of sodium and water, leading to less delivery of glomerular filtrate to ADH sensitive parts of renal tubule, and therefore lower urine volume results)

**Potassium Homeostasis**

- approximately 98% of total body  $\text{K}^+$  stores are intracellular
- normal serum  $\text{K}^+$  ranges from 3.5-5.0 mEq/L
- in response to  $\text{K}^+$  load, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia
- insulin, catecholamines, and acid-base status influence  $\text{K}^+$  movement into cells
  - aldosterone has a minor effect
- potassium excretion is regulated at the distal nephron
  - $\text{K}^+$  excretion = urine flow rate  $\times$  urine  $[\text{K}^+]$



$\text{Na}^+$  = predominating ion extracellular  
 $\text{K}^+$  = predominating ion intracellular

**Factors which Increase Renal  $\text{K}^+$  Loss**

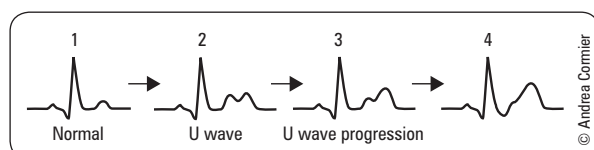
- hyperkalemia
- increased distal tubular urine flow rate and  $\text{Na}^+$  delivery (thiazides and loop diuretics)
- increased aldosterone activates epithelial sodium channel (eNaC) in cortical collecting duct, causing  $\text{Na}^+$  reabsorption and  $\text{K}^+$  excretion
- metabolic alkalosis
- hypomagnesemia
- increased non-reabsorbable anions in tubule lumen:  $\text{HCO}_3^-$ , penicillin, salicylate

**Hypokalemia**

- serum  $[\text{K}^+] < 3.5 \text{ mEq/L}$

**Signs and Symptoms**

- usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
- nausea, vomiting, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
- if severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
- arrhythmias occur at variable levels of  $\text{K}^+$ ; more likely if digoxin use, hypomagnesemia, or CAD
- ECG changes are more predictive of clinical picture than serum  $[\text{K}^+]$ 
  - U waves most important (low amplitude wave following a T wave)
  - flattened or inverted T waves
  - depressed ST segment
  - prolongation of Q-T interval
  - with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity



**Figure 5. ECG changes in hypokalemia**

### Approach to Hypokalemia

1. emergency measures: obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of  $K^+$  as cause of hypokalemia
3. assess contribution of dietary  $K^+$  intake
4. spot urine K:Cr (should be less than 1 in setting of hypokalemia)
  - if  $<1$  consider GI loss
  - if  $>1$  consider a renal loss
5. consider 24-h  $K^+$  excretion
6. if renal  $K^+$  loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum  $[Mg^{2+}]$

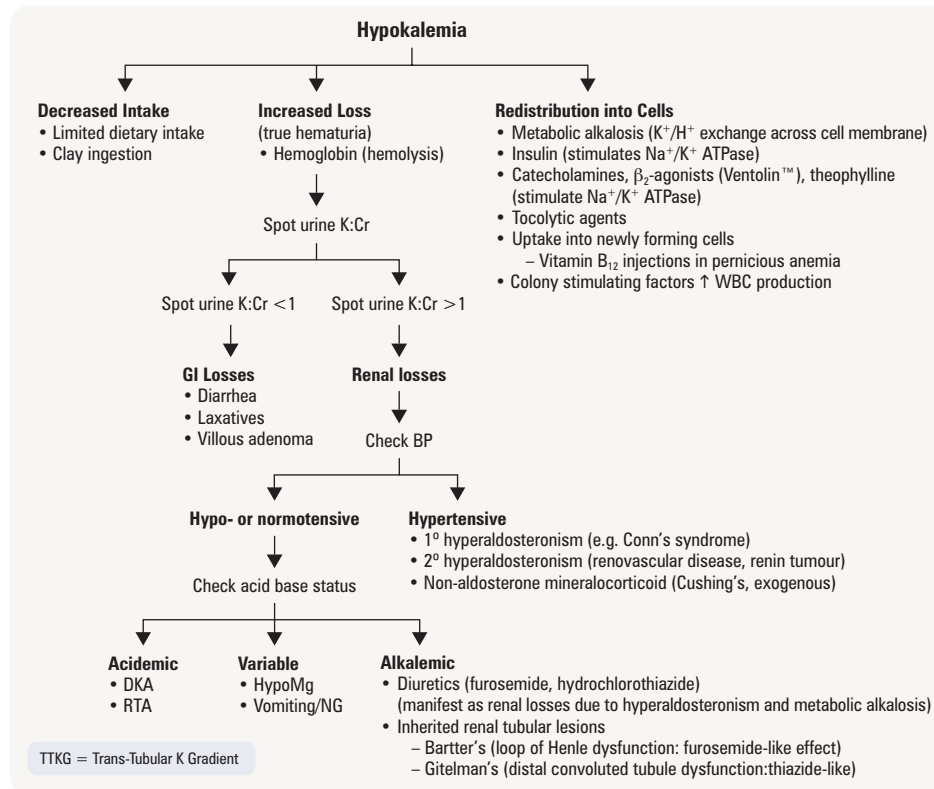


Figure 6. Approach to hypokalemia

### Treatment

- treat underlying cause
- if true  $K^+$  deficit, potassium repletion (decrease in serum  $[K^+]$  of 1 mEq is very roughly 100-200 mEq of total body loss)
  - oral sources – food, tablets (K-Dur®), KCl liquid solutions. Preferable route if the patient tolerates PO medications
  - IV – usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
  - max 40 mmol/L via peripheral vein, 60 mmol/L via central vein, max infusion 20 mmol/h
- $K^+$ -sparing diuretics (triamterene, spironolactone, amiloride) can prevent renal  $K^+$  loss
- restore  $Mg^{2+}$  if necessary
- if urine output and renal function are impaired, correct with extreme caution
- risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
- beware of excessive potassium repletion, especially if transcellular shift caused hypokalemia

## Hyperkalemia



- serum  $[K^+] > 5.0$  mEq/L

### Signs and Symptoms

- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniogenesis and metabolic acidosis

- ECG changes and cardiotoxicity (do not correlate well with serum  $[K^+]$ )
  - peaked and narrow T waves
  - decreased amplitude and eventual loss of P waves
  - prolonged PR interval
  - widening of QRS and eventual merging with T wave (sine-wave pattern)
  - AV block
  - ventricular fibrillation, asystole

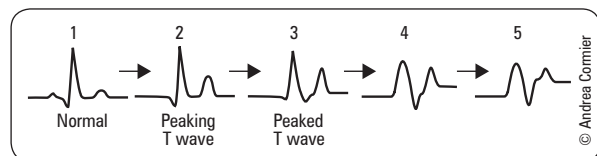


Figure 7. ECG changes in hyperkalemia

Table 8. Causes of Hyperkalemia

Factitious	Increased Intake	Cellular Release	Decreased Excretion
Sample hemolysis* Sample taken from vein where IV KCl is running Prolonged use of tourniquet Leukocytosis (extreme) Thrombocytosis (extreme)	Diet KCl tabs IV KCl Salt substitute	Intravascular hemolysis Rhabdomyolysis Insulin deficiency Hyperosmolar states (e.g. hyperglycemia) Metabolic acidosis (except for keto-and lactic acidosis) Tumour lysis syndrome Drugs <ul style="list-style-type: none"> <li><math>\beta</math>-blockers</li> <li>Digitalis overdose (blocks <math>Na^+/K^+</math> ATPase)</li> <li>Succinylcholine</li> </ul>	Decreased GFR <ul style="list-style-type: none"> <li>Renal failure</li> <li>Low effective circulating volume</li> <li>NSAIDs in renal insufficiency</li> </ul> Normal GFR but hypoaldosteronism (see Table 9)

\*Most common

**Drugs that Cause Hyperkalemia**

- $\beta$ -blockers
- Digitalis
- Succinylcholine

Table 9. Causes of Hyperkalemia with Normal GFR

Decreased Aldosterone Stimulus (low renin, low aldosterone)	Decreased Aldosterone Production (normal renin, low aldosterone)	Aldosterone Resistance (decreased tubular response)
Hyporeninemic, hypoaldosteronism <ul style="list-style-type: none"> <li>Associated with DM2, NSAIDs, chronic interstitial nephritis, HIV</li> </ul>	<ul style="list-style-type: none"> <li>Adrenal insufficiency of any cause (e.g. Addison's disease, AIDS, metastatic cancer)</li> <li>ACE inhibitors</li> <li>Angiotensin II receptor blockers</li> <li>Heparin</li> <li>Congenital adrenal hyperplasia with 21-hydroxylase deficiency</li> </ul>	<ul style="list-style-type: none"> <li><math>K^+</math>-sparing diuretics               <ul style="list-style-type: none"> <li>Spironolactone</li> <li>Amiloride</li> <li>Triamterene</li> </ul> </li> <li>Renal tubular disease</li> <li>Other <math>K^+</math>-sparing drugs               <ul style="list-style-type: none"> <li>Pentamidine</li> <li>Trimethoprim</li> <li>Cyclosporine, tacrolimus</li> <li>Pseudohypoaldosteronism (rare inherited tubular disorders)</li> </ul> </li> </ul>

**Approach to Hyperkalemia**

- emergency measures: obtain ECG, if life threatening begin treatment immediately
- rule out factitious hyperkalemia; repeat blood test
- hold exogenous  $K^+$  (PO and IV), and any  $K^+$  retaining medications
- assess potential causes of transcellular shift
- estimate GFR (calculate CrCl using Cockcroft-Gault)

**Treatment**

- acute therapy is warranted if ECG changes are present, or if patient is symptomatic
- tailor therapy to severity of increase in  $[K^+]$  and ECG changes
  - $[K^+] < 6.5$  and normal ECG
    - treat underlying cause, stop  $K^+$  intake, increase the loss of  $K^+$  via urine and/or GI tract (see below)
  - $[K^+] \text{ between } 6.5 \text{ and } 7.0$ , no ECG changes: add insulin to above regimen
  - $[K^+] > 7.0$  and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

**1. Protect the Heart**

- calcium gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes cardiac toxicity of hyperkalemia, protects cardiac conduction system, no effect on serum  $[K^+]$
- onset within minutes, lasts 30-60 min (N.B. May require repeat doses during treatment course of hyperkalemia)



In patients with diabetes and increased  $[K^+]$  and hyperglycemia, often just giving insulin to restore euglycemia is sufficient to correct the hyperkalemia.

**Treatment of Hyperkalemia****SEE BIG K DROP**

SEE – Calcium gluconate

BIG –  $\beta$ -agonist, Bicarb, Insulin, Glucose

K – Kayexalate®

DROP – Diuretics, Dialysis



## 2. Shift $K^+$ into Cells

- regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
  - onset of action 15-30 min, lasts 1-2 h
  - monitor capillary blood glucose q1h because of risk of hypoglycemia
  - can repeat every 4-6 h
  - caution giving D50W before insulin if hyperkalemia is severe as it can cause a serious arrhythmia
- $NaHCO_3$  1-3 ampules (given as 3 ampules of 7.5% or 8.4%  $NaHCO_3$  in 1L D5W)
  - onset of action 15-30 min, transient effect, drives  $K^+$  into cells in exchange for  $H^+$
  - more effective if patient has metabolic acidosis
- $\beta_2$ -agonist (Ventolin®) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  - onset of action 30-90 min, stimulates  $Na^+/K^+$  ATPase
  - caution if patient has heart disease as tachycardia may result from this high dose of  $\beta_2$ -agonist

## 3. Enhance $K^+$ Removal from Body

- via urine (preferred approach)
  - furosemide ( $\geq 40$  mg IV), may need IV NS to avoid hypovolemia
  - fludrocortisone (synthetic mineralocorticoid) if suspect aldosterone deficiency
- via gastrointestinal tract
  - cation-exchange resins: calcium resonium or sodium polystyrene sulfonate (Kayexalate®) (increasingly falling out of favor due to risk of colonic necrosis; works by binding  $Na^+$  in exchange for  $K^+$ , and controversial how much  $K^+$  is actually removed – main benefit may be the diarrhea it causes) plus lactulose PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered)
  - Kayexalate® enemas with tap water (and definitely not with sorbitol as rectal sorbitol can cause colonic necrosis)
- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

# Acid-Base Disorders

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic and CNS function
- see [Respirology](#), R5 for more information on respiratory acidosis/alkalosis
- normal concentration of  $HCO_3^-$  = 24 mEq/L (range: 22-30)
- normal  $pCO_2$  = 40 mmHg (range: 36-44)
- each acid base disorder has an appropriate compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder
  - e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis

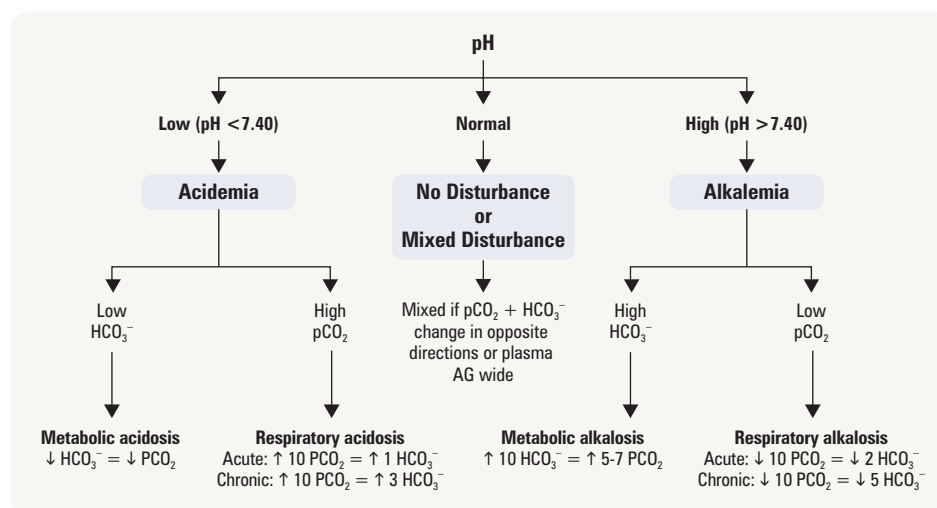


Figure 8. Approach to acid-base disorders

## Approach

### 1. Identify the primary disturbance (Figure 8)

- respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis

### 2. Evaluate compensation. If compensation is not appropriate, a second acid-base disorder is likely present

- compensation occurs in the same direction as the primary disturbance
- metabolic acidosis: for every 1 mmol/L decrease in  $\text{HCO}_3^-$ ,  $\text{pCO}_2$  should decrease by 1 mmHg
- metabolic alkalosis: for every 10 mmol/L increase in  $\text{HCO}_3^-$ ,  $\text{pCO}_2$  should increase by 5-7 mmHg
- respiratory acidosis: for every 10 mmHg increase in  $\text{pCO}_2$ ,  $\text{HCO}_3^-$  should increase by 1 (acute) or 3 (chronic) mmol/L
- respiratory alkalosis: for every 10 mmHg decrease in  $\text{pCO}_2$ ,  $\text{HCO}_3^-$  should decrease by 2 (acute) or 5 (chronic) mmol/L

### 3. Calculate Plasma Anion Gap (AG)

- $\text{AG} = [\text{Na}^+] - ([\text{HCO}_3^-] + [\text{Cl}^-])$
- baseline = 12, range 10-14
- AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 (e.g. if plasma [albumin] = 20 g/L, expect AG = 6)

### 4. If AG elevated, compare increase in AG with decrease in $\text{HCO}_3^-$

- if increase in AG < decrease in  $\text{HCO}_3^-$ , there is a coexisting non-AG metabolic acidosis
- if increase in AG > decrease  $\text{HCO}_3^-$ , there is a coexisting metabolic alkalosis

### 5. Calculate Osmolar Gap

- osmolar gap = measured osmolality – calculated osmolality
  - calculated osmolality =  $(2 \times [\text{Na}^+]) + [\text{urea}] + [\text{glucose}]$  (all units are in mmol/L)
  - normal osmolar gap <10
  - if AG >10, consider: methanol poisoning, ethylene glycol poisoning, OR another cause of acidosis plus ethanol ingestion



#### Useful Equations

- $\text{AG} = [\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$  (normal range = 10-14)
- Osmolar Gap = measured osmolality – calculated osmolality (normal <10)
- Calculated Osmolality =  $2[\text{Na}^+] + [\text{Urea}] + [\text{Glucose}]$

## Metabolic Acidosis

### Etiology and Pathophysiology

#### 1. Increased AG Metabolic Acidosis (4 types)

- Lactic acidosis (2 types)
  - L-lactic acid
    - Type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
    - Type B: non-hypoxic – multiple causes. The most common is failure to metabolize normally produced lactic acid in the liver due to severe liver disease. Other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain antiretrovirals, large tumours, mitochondrial myopathies
  - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
    - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria that produce D-lactic acid, a carbohydrate load, diminished colonic motility and impaired D-lactate metabolism
- Ketoacidosis
  - diabetic
  - starvation
  - alcoholic (decreased carbohydrate intake and vomiting)
- Toxins
  - methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
  - ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
  - salicylate (e.g. ASA) overdose, causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacid (salicylate activates fat breakdown)
- Advanced renal failure (i.e. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)



#### Causes of Increased Anion Gap Metabolic Acidosis

##### MUDPILES

Methanol  
Uremia  
Diabetic/alcoholic/starvation ketoacidosis  
Paraldehyde  
Isopropyl alcohol/Iron  
Lactic acidosis  
Ethylene glycol  
Salicylates

or

##### KARMEL

Ketoacidosis  
ASA  
Renal Failure  
Methanol  
Ethylene Glycol  
Lactic Acidosis

## 2. Normal AG Metabolic Acidosis (Hyperchloremic Acidosis)

- diarrhea ( $\text{HCO}_3^-$  loss from GI tract)
- RTA (renal tubular acidosis)
  - type I RTA (distal): inability to secrete  $\text{H}^+$  in collecting duct, leading to impaired excretion of ammonium into urine
  - type II RTA (proximal): impaired  $\text{HCO}_3^-$  reabsorption
  - type IV RTA: defective ammoniogenesis due to decreased aldosterone, hyporesponsiveness or hyperkalemia
- to help distinguish renal causes from non-renal causes, use Urine Anion Gap =  $(\text{Na}^+ + \text{K}^+) - \text{Cl}^-$
- calculation establishes the presence or absence of unmeasured positive ions (e.g.  $\text{NH}_4^+$ ) in urine
  - if  $<0$ , suggests adequate  $\text{NH}_4^+$  in urine (likely nonrenal cause: diarrhea)
  - if  $>0$ , suggests problem is lack of  $\text{NH}_4^+$  in urine (e.g. distal RTA)

## Treatment of Metabolic Acidosis

- treat underlying cause
  - insulin for DKA
  - restore tissue perfusion for Type A lactic acidosis
  - ethanol + dialysis for methanol or ethylene glycol poisoning
  - alkaline diuresis  $\pm$  dialysis if ASA overdose
- correct coexisting disorders of  $\text{K}^+$  (see *Hyperkalemia*, NP12)
- consider treatment with exogenous alkali (e.g.  $\text{NaHCO}_3$ ) if:
  - severe reduction in  $[\text{HCO}_3^-]$  e.g.  $<8$  mmol/L, especially with very low pH ( $<7$ )
  - no metabolizable anion (e.g. salicylate, formate, oxalate, sulphate, since these cannot be further metabolized)
- note: lactate and ketoacid anions can be metabolized to  $\text{HCO}_3^-$
- risks of sodium bicarbonate therapy
  - hypokalemia: causes  $\text{K}^+$  to shift into cells (correct  $\text{K}^+$  deficit first)
  - ECF volume overload:  $\text{Na}^+$  load given with  $\text{NaHCO}_3$ , can exacerbate pulmonary edema
  - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to  $\text{HCO}_3^-$  and persisting hyperventilation



### Causes of Non-Anion Gap Metabolic Acidosis

#### HARDUP

Hyperalimentation  
Acetazolamide  
RTA\*  
Diarrhea\*  
Ureteroenteric fistula  
Pancreaticoduodenal fistula increased

\*Most common



### 3 Clinical Scenarios that Produce a Mixed Disorder with Near Normal pH

(i.e. increased PAG metabolic acidosis + resp. alkalosis)

- Cirrhosis
- ASA overdose
- Sepsis

## Metabolic Alkalosis

### Pathophysiology

- requires initiating event and maintenance factors
- precipitating factors
  - GI (vomiting, NG tube) or renal loss of  $\text{H}^+$
  - exogenous alkali (oral or parenteral administration), milk alkali syndrome
  - diuretics (contraction alkalosis): decreased excretion of  $\text{HCO}_3^-$ , decreased ECF volume, therefore increased  $[\text{HCO}_3^-]$
  - post-hypercapnia: renal compensation for respiratory acidosis is  $\text{HCO}_3^-$  retention, rapid correction of respiratory disorder results in transient excess of  $\text{HCO}_3^-$
- maintenance factors
  - volume depletion: increased proximal reabsorption of  $\text{NaHCO}_3^-$  and increased aldosterone
  - hyperaldosteronism ( $1^\circ$  or  $2^\circ$ ): distal  $\text{Na}^+$  reabsorption in exchange for  $\text{K}^+$  and  $\text{H}^+$  excretion leads to  $\text{HCO}_3^-$  generation; aldosterone also promotes hypokalemia
  - hypokalemia: transcellular  $\text{K}^+/\text{H}^+$  exchange, stimulus for ammoniogenesis and  $\text{HCO}_3^-$  generation

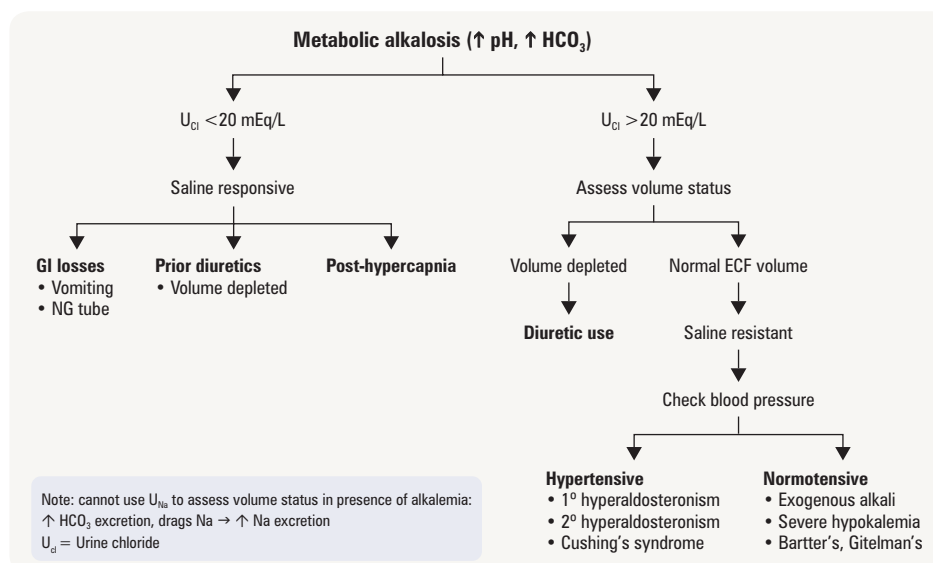


Figure 9. Approach to metabolic alkalosis

**Evaluate Compensation (identify co-existing respiratory acid-base disorders)**

- hypoventilation (an upper limit to compensation exists – breathing cannot be stopped; see Figure 9)

**Treatment**

- treat underlying cause
- correct underlying disease, replenish  $K^+$  and  $Mg^{2+}$  deficits, and possibly  $K^+$ -sparing diuretic
- saline sensitive metabolic alkalosis (most common)
  - treatment: volume repletion
  - $\pm$  carbonic anhydrase inhibitor (e.g. acetazolamide) to facilitate loss of  $HCO_3^-$  in urine
- saline resistant metabolic alkalosis
  - ECF volume normal or high
  - usually aldosterone or glucocorticoid excess
  - remove source of aldosterone or glucocorticoid  $\pm$  spironolactone

## Vascular Diseases of the Kidney

### Large Vessel Disease

**Table 10. Summary of Vascular Diseases**

Large Vessel Disease	Small Vessel Disease
Acute renal artery occlusion (infarct)	Hypertensive nephrosclerosis
Renal artery stenosis (ischemia)	Atheroembolic renal disease
Renal vein thrombosis	Thrombotic microangiopathy
	Scleroderma
	Calcineurin inhibitor nephropathy

**1. RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)**

- important, potentially reversible cause of renal failure

**Etiology**

- abdominal trauma, surgery, embolism, vasculitis, extra-renal compression, hypercoagulable state, aortic dissection
- kidney transplant more vulnerable

**Signs and Symptoms (depend on presence of collateral circulation)**

- fever, nausea, vomiting, flank pain
- leukocytosis, elevated AST, ALP
- marked elevated LDH (LDH  $>4$  times upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
- acute onset hypertension (activation of RAAS) or sudden worsening of long-standing hypertension
- renal dysfunction, i.e. elevated Cr (if bilateral, or solitary functioning kidney)

**Investigations**

- renal arteriography (more reliable but risk of atheroembolic renal disease)
- contrast-enhanced CT or magnetic resonance angiography, duplex Doppler studies (operator dependent)

**Treatment**

- prompt localization of occlusion and restoration of blood flow
- anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
- medical therapy in the long-term to reduce risk (e.g. antihypertensives)

**2. ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)**

- chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
- significant cause of ESRD: 15% in patients over 50 yr old (higher prevalence if significant vascular disease)
- usually associated with large vessel disease elsewhere
- causes of renal artery stenosis:
  - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males  $>55$  yr, smokers
    - ♦ electrolytes, osmolality (gently rehydrate when needed, i.e. CHF)
  - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset  $<30$  yr) (gently rehydrate when needed, i.e. CHF)
- when there is decreased renal blood flow (RBF), GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the filtration fraction (GFR/RBF)

- most common cause of secondary hypertension ("renovascular hypertension"), 1-2% of all hypertensive patients
  - etiology
    - ♦ decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
    - ♦ increased angiotensin raises blood pressure in two ways
      1. causes generalized arteriolar constriction
      2. release of aldosterone increases  $\text{Na}^+$  and water retention
  - elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN

**Risk Factors**

- >50 yr old
- smoking
- other atherosclerotic disease (dyslipidemia, diabetes, diffuse atherosclerosis)

**Signs and Symptoms**

- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

**Investigations**

- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (i.e. captopril renal scan)
- renal arteriography (gold standard)

**Treatment**

- surgical: percutaneous angioplasty  $\pm$  stent, surgical revascularization, occasionally surgical bypass
- medical: BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- little or no benefit if therapy is late i.e. kidney is already shrunk (however, therapy can be considered to save the opposite kidney if normal)

**3. RENAL VEIN THROMBOSIS****Etiology**

- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical presentation determined by rapidity of occlusion and formation of collateral circulation

**Signs and Symptoms**

- acute: nausea/vomiting, flank pain, hematuria, elevated plasma LDH,  $\pm$  rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria and/or tubule dysfunction

**Investigations**

- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

**Treatment**

- thrombolytic therapy  $\pm$  percutaneous thrombectomy for acute RVT
- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

**Revascularization versus Medical Therapy for Renal-Artery Stenosis**

NEJM 2009;361:1953-1962

**Study:** Multicentre, un-blinded RCT, median follow-up of 34 mo.

**Patients:** 806 patients (mean age 70) with atherosclerotic stenosis in at least one renal artery and uncertain clinical benefit of revascularization.

**Intervention:** Percutaneous revascularization (angioplasty and/or stenting) with medical therapy (i.e. statins, antiplatelet, BP control) versus medical therapy alone.

**Outcomes:** Primary outcome was change in renal function (slope of creatinine concentration over time). Secondary outcomes include BP, time to first renal event, time to first CV event, and mortality.

**Results:** No significant difference in change of renal function between intervention and medical therapy control. No significant differences in any secondary outcomes were found between revascularization and medical therapy control. 31 patients (9%) experienced a periprocedural complication, and 55 patients (20%) experienced a post-procedural complication.

**Conclusion:** Renal artery revascularization carries significant risks without any benefit to renal function or secondary outcomes compared to medical therapy.

## Small Vessel Disease

**1. HYPERTENSIVE NEPHROSCLEROSIS**

- see *Hypertension*, NP30

**2. ATHEROEMBOLIC RENAL DISEASE**

- progressive renal insufficiency due to embolic obstruction of small and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)

- anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
- investigations:
  - eosinophilia, eosinophiluria and hypocomplementia
  - renal biopsy: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small/medium-sized vessels
- treatment:
  - no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
- prognosis: poor overall, at least a third will develop ESRD

### 3. THROMBOTIC MICROANGIOPATHY

- etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
- treatment:
  - depends on cause
  - supportive therapy
  - TTP-HUS: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)
- avoid platelet transfusions and ASA

### 4. CALCINEURIN INHIBITOR NEPHROPATHY

- cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplant (e.g. heart)
- acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
  - pre-renal azotemia
  - treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
- chronic: result of obliterative arteriopathy causing interstitial nephritis and CRF (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors



#### Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation (ELITE-Symphony Trial) *NEJM* 2007;257:2562-2575

**Study:** Multicentre, randomized controlled trial with 12 mo follow-up.

**Patients:** 1645 patients scheduled to receive a single organ kidney transplant.

**Intervention:** Mycophenolate mofetil, corticosteroids and either: 1) standard dose cyclosporine; 2) low dose cyclosporine with daclizumab induction; 3) low dose tacrolimus with daclizumab induction; 4) low dose sirolimus with daclizumab induction.

**Primary Outcome:** Estimated Cockcroft-Gault GFR 12 mo after transplantation.

**Results:** the Tacrolimus arm showed significantly higher eGFR at 12 mo compared to all other arms (65.4 mL/min vs. 57.1, 59.4, 56.7 for arms 1, 2, 4 respectively,  $p < 0.001$ ). The Tacrolimus arm also showed decreased rates of acute rejection at 6 mo and 12 mo vs. all arms ( $p < 0.001$ ); improved allograft survival against standard dose cyclosporine and sirolimus; and decreased treatment failure against all other arms. There was no difference in overall patient survival between groups. Sirolimus has the highest incidence of lymphoceles, delayed wound healing, and serious adverse events; tacrolimus has significantly higher rates of new-onset diabetes; and cyclosporine regimes had the lowest incidence of diarrhea but highest opportunistic infection rates.

**Conclusion:** Immunosuppression regimens using low dose tacrolimus and daclizumab induction decrease nephrotoxicity while maintaining therapeutic immunosuppression in renal transplant patients.

## Glomerular Disease

### Histological Terms of Glomerular Changes

#### Extent of Changes

- terms used to describe histologically the number of glomeruli affected in a given condition:
  - diffuse: majority of glomeruli abnormal (>50%)
  - focal: some glomeruli affected
- terms used to describe histologically the extent to which individual glomeruli are affected in a given condition:
  - global: entire glomerulus abnormal
  - segmental: only part of the glomerulus abnormal

#### Types of Changes

- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane
- crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration form crescent-shape in Bowman's space

### Clinical Presentation of Glomerular Disease

#### Important Points to Remember

- glomerular disease has diverse clinical presentations including hematuria, proteinuria, hypertension, edema and decreased GFR
  - each glomerulopathy presents as one of four major glomerular syndromes (these are NOT diagnoses):
    - ♦ acute nephritis
    - ♦ rapidly progressive glomerulonephritis
    - ♦ nephrotic
    - ♦ asymptomatic urinary abnormalities



- glomerulopathies can be caused by a primary disease OR can occur secondary to a systemic disease
- some glomerulopathy can present as more than one syndrome at different times

### The Nephritic-Nephrotic Spectrum

- glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes (see Figure 10)

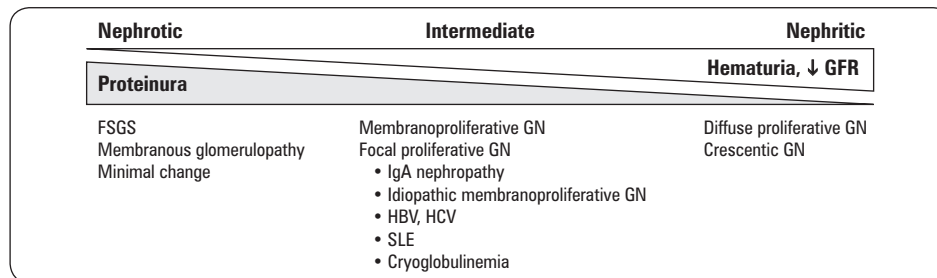


Figure 10. Spectrum of glomerular pathology

### PROTEINURIA

- hallmark of nephrotic syndromes
- 24-h urine protein: gold standard to assess degree of proteinuria
- urine albumin-to-creatinine ratio (ACR): used to screen for diabetic nephropathy
  - microalbuminuria
    - defined as ACR  $\geq 2.8$  mg/mmol (female) or  $\geq 2.0$  mg/mmol (male)
    - marker of vascular endothelial function
    - an important prognostic marker for kidney disease in diabetes and hypertension (see *Diabetes*, NP28)
  - an elevated ACR  $\geq 2.0$  or 2.8 mg/mmol is the earliest sign of diabetic nephropathy
- composition of normal total urine protein
  - upper limit of normal daily excretion of total protein is 150 mg/d
  - upper limit of normal daily excretion of albumin is 30 mg/d
  - the other normally excreted proteins are either filtered low molecular weight proteins (such as immunoglobulin, light chains or  $\beta$ -2 microglobulin) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)

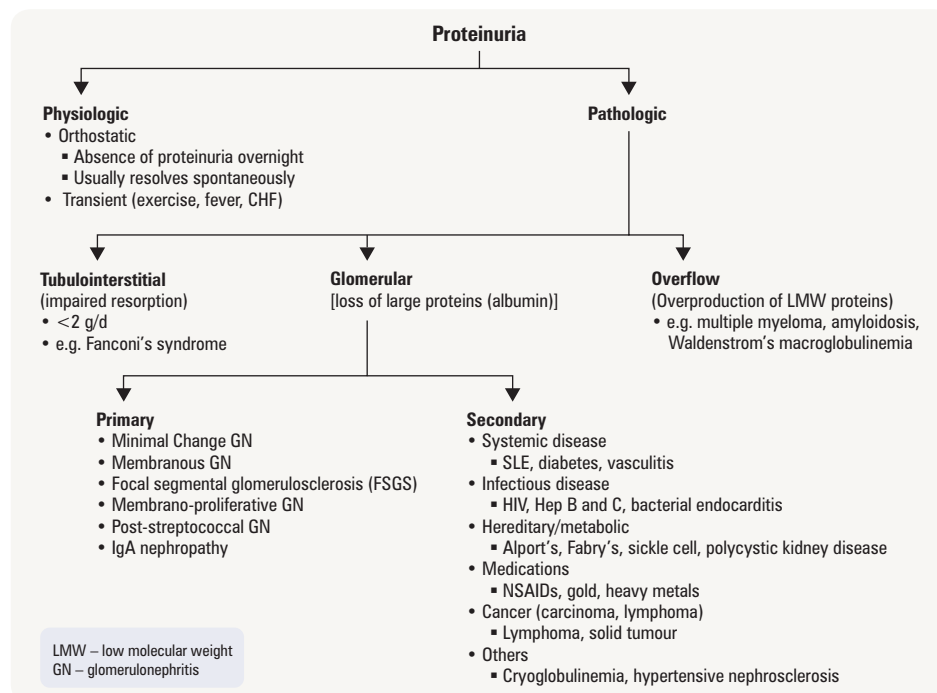


Figure 11. Classification of proteinuria



### PATHOLOGIC PROTEINURIA

#### Tubulointerstitial

- Normally low molecular weight (LMW) proteins (<60 kD) pass through glomerular filtration barrier and are reabsorbed in proximal tubule
- Proximal tubule dysfunction causes impaired reabsorption and increased excretion of LMW proteins
- Albumin (>60 kD) is NOT affected. Thus, edema is partly secondary to salt and water retention

#### Glomerular

- Normally, the filtration barrier is selectively permeable to SIZE (<60 kD) and CHARGE (repels negative particles). Thus, albumin is filtered to a very limited extent through a normal glomerulus
- Damage to any component of the glomerular filtration barrier results in loss of albumin and other high MW proteins. Thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (possibly due to filtered proteins stimulating the action of cortical collecting duct epithelial sodium channel)

#### Overflow

- Increased production of LMW proteins which exceeds the reabsorptive capacity of the proximal tubule
- Plasma cell dyscrasias: produce light chain Ig (multiple myeloma, Waldenstrom's macroglobulinemia, monoclonal gammopathy of undetermined significance)

**Table 11. Daily Excretion of Protein**

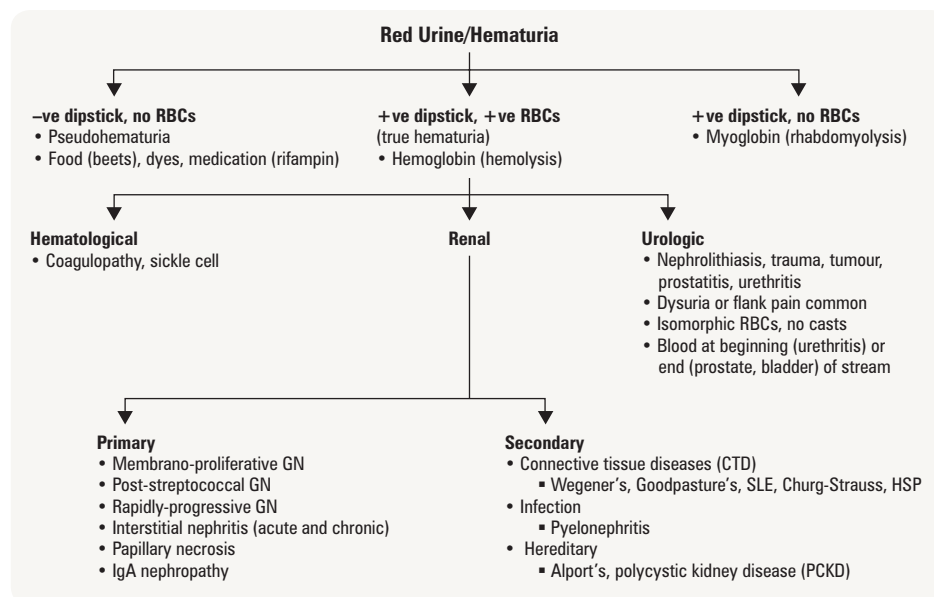
Daily Excretion	Meaning
<150 mg total protein (and <30 mg albumin)	Normal
30-300 mg albumin	Microalbuminuria
>3500 mg total protein /1.73m <sup>2</sup> BSA	Nephrotic range proteinuria
Variable amount of proteinuria	Can be seen with glomerular disease; i.e. mild glomerular disease can lead to a mild degree of proteinuria, proliferative lesions may also be associated with some degree of proteinuria
Up to 2000 mg per d	Possible tubular disease because of failure to reabsorb filtered proteins

**Investigations**

- urine R&M, C&S, urea, Cr
- further workup (if degree of proteinuria >0.5 g/d, casts and/or hematuria)
  - CBC, glucose, electrolytes, 24-h urine protein and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic ultrasound
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA, (PR3) Hep B, Hep C, HIV, Anti-steptolysin-O (ASOT)
- indications for nephrology referral
  - generally, if there is “heavy” proteinuria, should refer to nephrologist
  - heavy proteinuria is ACR >30 mg/mmol
- definitely if there is nephrotic syndrome: marked proteinuria >3.5 g/1.73m<sup>2</sup>/d with hypoalbuminemia (<35 g/L)

**HEMATURIA**

- hallmark of nephritic syndromes
- presence of blood or RBCs in urine
  - gross hematuria: pink, red, or tea-coloured urine
    - ♦ in gross hematuria, the urine should be centrifuged:
      - if the sediment is red, true hematuria.
      - if the supernatant is red, test for heme with a dipstick
        - if supernatant +ve for heme: myoglobinuria or hemoglobinuria
        - if –ve for heme: pseudohematuria. Consider medications (e.g. rifampin), food dyes (e.g. beets) or metabolites (e.g. porphyria)
- microscopic hematuria: normal coloured urine, >2-3 RBCs/HPF on microscopy

**Figure 12. Approach to red urine****Investigations for Hematuria**

- Hx and Px: family history of nephrolithiasis, hearing loss (Alport's), cerebral aneurysm (PCKD), diet, recent URTI, irritative and obstructive urinary symptoms (UTI)
- urine R&M, C&S, urea, Cr
- renal ultrasound
- 24-h urine stone workup if there is a history of stone formation or if there is a stone noted on imaging: calcium, oxalate, citrate, magnesium, uric acid, cysteine

- further workup (if casts and/or proteinuria): CBC, electrolytes, 24-h urine protein and Cr, serology (ANA, RF, C3, C4, p-ANCA, c-ANCA, ASOT)
- consider urology consult and possible cystoscopy if not clearly a nephrologic source for hematuria or if >50 yr of age

## Glomerular Syndromes

### 1. Acute NEPHRITIC SYNDROME

- a subset of nephritic syndrome in which the clinical course proceeds over days

#### Etiology

- etiology can be divided into low and normal complement levels (Figure 13)
- frequently immune-mediated, with Ig and C3 deposits found in GBM
- outcome dependent on etiology

#### Clinical/Lab Features

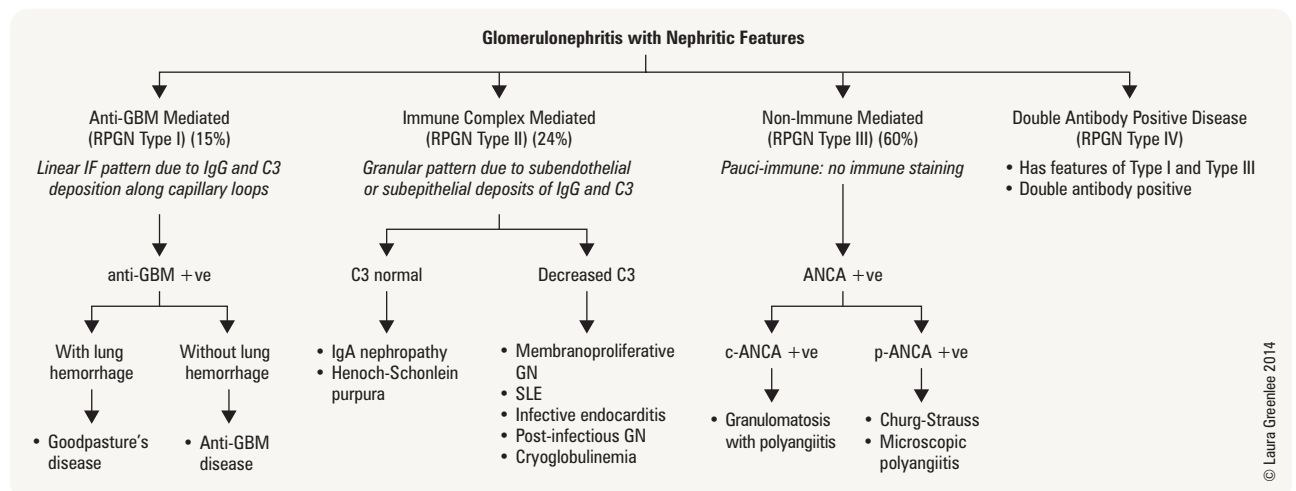
- proteinuria (but <3.5 g/1.73 m<sup>2</sup>/d), abrupt onset hematuria (microscopic or macroscopic, azotemia (increased Cr and urea), RBC casts and/or dysmorphic RBCs in urine, oliguria, HTN (due to salt and water retention), peripheral edema/puffy eyes, smoky urine (see sidebar)



#### Features of Nephritic Syndrome

##### PHAROH

Proteinuria  
Hematuria  
Azotemia  
RBC casts  
Oliguria  
Hypertension



© Laura Greenlee 2014

Figure 13. Approach to nephritic syndrome

### 2. RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (Rpgn)/ CRESCENTIC GLOMERULONEPHRITIS

- a subset of nephritic syndrome in which the clinical course proceeds over weeks to months
- clinical diagnosis, not histopathological
- any cause of glomerulonephritis can present as RPGN (except minimal change disease)
- additional etiologies seen only as RPGN: Goodpasture's syndrome and granulomatosis with polyangiitis (previously called Wegener's granulomatosis)

#### Clinical/Lab Features

- fibrous crescents typically present on renal histopathology
- RBC casts and/or dysmorphic RBCs in urine
- classified by immunofluorescence staining (see Figure 13)
- Type I: Anti-GBM mediated (15% of cases)
- Type II: Immune Complex Mediated (24% of cases)
- Type III: Non-Immune Mediated (60% of cases)
- Type IV: Double Antibody Positive (see Figure 13)
- treatment: underlying cause for postinfectious; corticosteroids + cyclophosphamide or other cytotoxic agent + plasmaphoresis in select cases
- prognosis: 50% recovery with early treatment, depends on underlying cause

### 3. NEPHROTIC SYNDROME

#### Clinical/Lab Features

- heavy proteinuria (>3.5 g/1.73m<sup>2</sup>/d)
- hypoalbuminemia
- edema

- hyperlipidemia (elevated LDL cholesterol), lipiduria (fatty casts and oval fat bodies on microscopy)
- hypercoagulable state (due to antithrombin III, Protein C and Protein S urinary losses)
- patient may report frothy urine
- glomerular pathology on renal biopsy:
  - minimal change disease (or minimal lesion disease or nil disease) – i.e. glomeruli appear normal on light microscopy
  - membranous glomerulopathy
  - focal segmental glomerulosclerosis (FSGS)
  - membranoproliferative glomerulonephritis
  - nodular glomerulosclerosis
- each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause proteinuria without obvious glomerular pathology)



#### Presentation of Nephrotic Syndrome

##### HELP

Hypoalbuminemia  
Edema  
Lipid abnormalities  
Proteinuria

**Table 12. Nephrotic Syndrome**

	Minimal Change	Membranous Glomerulopathy	Focal Segmental Glomerulosclerosis	Membranoproliferative Glomerulonephritis	Nodular Glomerulosclerosis
<b>Secondary Causes</b>	Hodgkin's lymphoma	HBV, SLE, solid tumours (lung, breast, GI)	Reflux nephropathy, HIV, HBV, obesity	HCV, malaria, SLE, leukemia, lymphoma, infected shunt	Diabetes mellitus, amyloidosis
<b>Drug Causes</b>	NSAIDs	Gold, penicillamine	Heroin		
<b>Therapy</b>	Steroids	Reduce BP, ACEI, steroids	Steroids, ACEI/ARB for proteinuria	Aspirin <sup>®</sup> , ACEI, dipyridamole (Persantine <sup>®</sup> ) – controversial	Treat underlying cause

## 4. ASYMPTOMATIC URINARY ABNORMALITIES

### Clinical/Lab Features

- proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
  - isolated proteinuria
    - ♦ can be postural
    - ♦ occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
  - hematuria with or without proteinuria
    - ♦ IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, usually presents after viral URTI
    - ♦ hereditary nephritis (Alport's disease): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/d
    - ♦ thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
    - ♦ benign recurrent hematuria: hematuria associated with febrile illness, exercise or immunization; a diagnosis of exclusion after other possibilities are ruled out



IgA nephropathy is the most common type of primary glomerular disease worldwide.

## Investigations for Glomerular Disease

- blood work
  - first presentation: electrolytes, Cr, urea, albumin, fasting lipids
  - determining etiology: CBC, ESR, serum immunoelectrophoresis, anti-GBM, C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV
- urinalysis: RBCs, WBCs, casts, protein
- 24-h urine for protein and CrCl
- radiology
  - CXR (infiltrates, CHF, pleural effusion)
  - renal ultrasound
- renal biopsy (percutaneous or open) if heavy proteinuria or renal insufficiency, and cause not obviously diabetic nephropathy
- urine immunoelectrophoresis
  - for Bence-Jones protein if proteinuria present

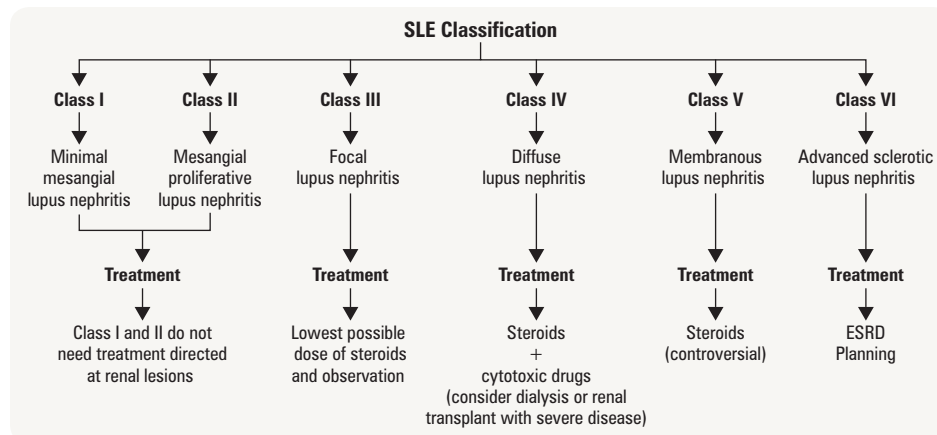
## Secondary Causes of Glomerular Disease

### Amyloidosis

- nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
- presents as nephrotic range proteinuria with progressive renal insufficiency
- can be primary or secondary
- secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy

## Systemic Lupus Erythematosus (SLE)

- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- glomerulonephritis caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis



**Figure 14. International Society of Nephrology/Renal Pathology Society classification of lupus nephritis 2003**

## Henoch-Schönlein Purpura (HSP)

- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia and fever
- glomeruli show varying degrees of mesangial hypercellularity
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

## Goodpasture's Disease

- antibodies against type IV collagen present in lungs and GBM
- more common in 3rd and 6th decades of life, men slightly more affected than females
- present with RPGN type I and hemoptysis/dyspnea
- pulmonary hemorrhage more common in smokers and males
- treat with plasma exchange, cyclophosphamide, prednisone

## ANCA Associated Vasculitis [i.e. Granulomatosis with Polyangiitis and Microscopic Polyangiitis (formerly Wegener's Granulomatosis)]

- pr3-ANCA (c-ANCA) most commonly associated with the clinical picture of granulomatosis with polyangiitis (previously called Wegener's granulomatosis)
- mpo-ANCA (p-ANCA) most commonly associated with the clinical picture of microscopic polyangiitis
- renal involvement very common
- focal segmental necrotizing RPGN with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treating typically involves cyclophosphamide and prednisone

## Cryoglobulinemia

- cryoglobulins: monoclonal IgM and polyclonal IgG
- presents as purpura, fever, Raynaud's phenomenon and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

## Shunt Nephritis

- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients



### EULAR Recommendations for the Management of Systemic Lupus Erythematosus (SLE)

*Ann Rheum Dis* 2008;67:195-205

#### Lupus Nephritis Recommendations

**Monitoring:** Renal biopsy, urine sediment analysis, proteinuria, and kidney function may have independent predictive ability for clinical outcome in therapy of lupus nephritis but need to be interpreted in conjunction. Changes in immunological tests (anti-dsDNA, serum C3) have only limited ability to predict the response to treatment and may be used only as supplemental information.

**Treatment:** In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens, which are however associated with considerable adverse effects. In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and a more favourable toxicity profile: failure to respond by 6 mo should evoke discussions for intensification of therapy. Flares following remission are not uncommon and require diligent follow-up.

**End-stage renal disease:** Dialysis and transplantation in SLE have long-term patient and graft-survival rates comparable with those observed in non-diabetic non-SLE patients, with transplantation being the method of choice.

**HIV-Associated Renal Disease**

1. direct nephrotoxic effect of HIV infection, antiretroviral drugs (e.g. tenofovir, indinavir) and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy (HIVAN)
  - histology: focal and segmental glomerular collapse with mesangial sclerosis, “collapsing FSGS”
  - tubular cystic dilation and tubulo-reticular inclusions
  - clinical features: predominant in black men, heavy proteinuria, progressive renal insufficiency
  - prognosis: kidney failure within 1 yr without treatment
  - therapy: short-term, high dose steroids, ACEI, HAART

**Infective Endocarditis**

- manifests as mild form of acute nephritic syndrome with decreased serum complement
- *S. aureus* is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

**Hepatitis B**

- can result in membranous nephropathy, polyarteritis nodosa, membranoproliferative GN

**Hepatitis C**

- can result in membranoproliferative GN, cryoglobulinemia and membranous nephropathy

**Syphilis**

- can result in membranous GN

## Tubulointerstitial Disease



### Tubulointerstitial Nephritis (TIN)

**Definition**

- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

**Signs and Symptoms**

- manifestation of disease depends on site of tubule affected
  1. proximal tubule (e.g. multiple myeloma, heavy metals)
    - ♦ Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hypouricemia
    - ♦ proximal RTA (decreased bicarbonate absorption): Type II RTA
  2. distal tubule (e.g. amyloidosis, obstruction)
    - ♦ distal RTA (Type I RTA), usually hypokalemic
    - ♦  $\text{Na}^+$ -wasting nephropathy
    - ♦  $\pm$  hyperkalemia leading to type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
  3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
    - ♦ urinary concentrating defect leading to mild nephrogenic DI
    - ♦ polyuria

**1. ACUTE TUBULOINTERSTITIAL NEPHRITIS (TIN)****Definition**

- rapid (days to weeks) decline in renal function
- 10-20% of all acute kidney injury

**Etiology**

- hypersensitivity
  1. antibiotics:  $\beta$ -lactams, sulfonamides, rifampin, quinolones, cephalosporins
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
- infections
  - bacterial pyelonephritis, *Streptococcus*, brucellosis, *Legionella*, CMV, EBV, toxoplasmosis, leptospirosis
- immune
  - SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia
- idiopathic

**Pathophysiology**

- acute inflammatory cell infiltrates into renal interstitium



**Signs and Symptoms**

- AKI
- if hypersensitivity reaction: may see fever, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
- if pyelonephritis: flank pain and costo-vertebral angle (CVA) tenderness
- other signs and symptoms based on underlying etiology
- hypertension and edema are uncommon

**Investigations**

- mild, non-nephrotic range proteinuria and microscopic hematuria
- urine
  - sterile pyuria, WBC casts, mild proteinuria, hematuria
  - eosinophils if allergic interstitial nephritis
- blood
  - increased Cr and urea
  - eosinophilia if drug reaction
  - normal AG metabolic acidosis (RTA)
  - hypophosphatemia, hyperkalemia, hyponatremia
- gallium scan often shows intense signal due to inflammatory infiltrate
- renal biopsy definitive

**Treatment**

- treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

**Prognosis**

- recovery within 2 wk if underlying insult can be eliminated
- the longer the patient is in renal failure, the less likely full renal recovery becomes

**2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS****Definition**

- characterized by slowly progressive renal failure, moderate proteinuria and signs of abnormal tubule function

**Etiology**

- persistence or progression of acute TIN
- urinary tract obstruction: most important cause of chronic TIN (tumours, stones, bladder outlet obstruction, vesicoureteral reflux)
- chronic pyelonephritis due to vesicoureteral reflux or UTI with obstruction
- nephrotoxins
  - exogenous
    - ♦ analgesics: NSAIDs (common), acetaminophen
    - ♦ cisplatin, lithium, cyclosporine, tacrolimus
    - ♦ heavy metals (lead, cadmium, copper), lithium, mercury, arsenic
    - ♦ radiation
    - ♦ chinese herbs
  - endogenous
    - ♦ hypercalcemia, hypokalemia, oxalate, uric acid nephropathy
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma, lymphoma
- granulomatous: TB, sarcoidosis, granulomatosis with polyangiitis
- immune: SLE, Sjögren's, cryoglobulinemia, Goodpasture's, amyloidosis, renal graft rejection, vasculitis
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

**Pathophysiology**

- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

**Signs and Symptoms**

- tubular dysfunction (e.g. acidosis, electrolyte disturbances)
- progressive renal failure with azotemia and uremia
- dependent on underlying etiology

**Treatment**

- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders ( $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$ ) and anemia

### Findings which Suggest Chronic Tubulointerstitial Nephritis

- normal AG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi's syndrome
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- ultrasound: shrunken kidneys with irregular contours

## Acute Tubular Necrosis (ATN)

### Definition

- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

### Etiology

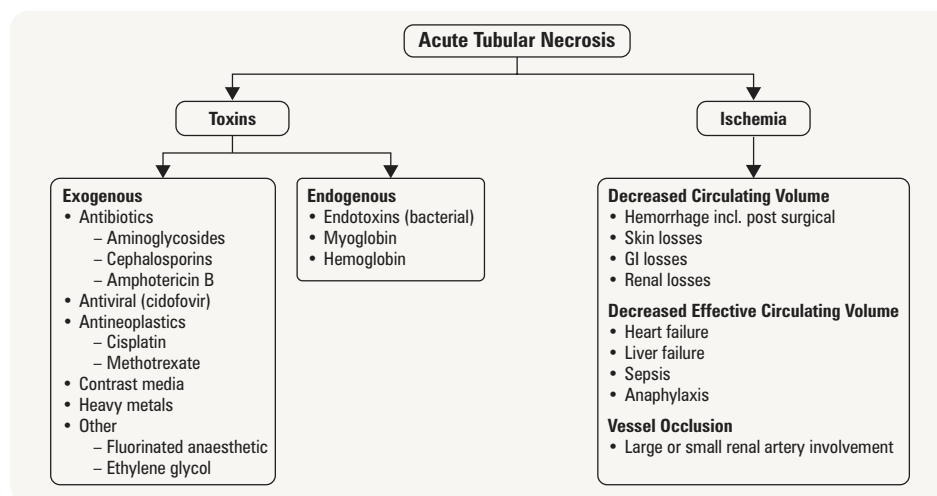


Figure 15. Etiology of ATN

### Clinical Presentation

- typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
- urine: high  $\text{FE}_{\text{Na}^+}$ , pigmented-granular casts

### Complications

- hyperkalemia: can occur rapidly and cause serious arrhythmias
- metabolic acidosis, decreased  $\text{Ca}^{2+}$ , increased  $\text{PO}_4^{3-}$ , hypoalbuminemia

### Investigations

- blood: CBC, electrolytes, Cr, urea,  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$ , blood gases
- urine: R&M, electrolytes, osmolality, microscopic urinalysis searching for pigmented granular casts
- ECG
- abdominal ultrasound
- rule out other causes of pre-renal/post-renal azotemia and intrinsic AKI (GN, AIN, vasculitis)

### Therapy

- largely supportive once underlying problem is corrected
- loop diuretics may help manage volume overload and reduce tubular metabolic requirements to allow for recovery (controversial)
- consider early dialysis in severe/rapidly progressing cases to prevent uremic syndrome

### Prevention

- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast:
  - give N-acetylcysteine 600-1200 mg PO bid day before and day of procedure, give intravenous isotonic fluid (either NaCl or  $\text{NaHCO}_3$ )
  - isotonic  $\text{NaHCO}_3$  at 3 mL/kg over 1h before procedure and 1 mL/kg/h for 6 h post-procedure if not contraindicated
  - avoid giving diuretics, ACEI, cyclosporine on morning of procedure if possible
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency



#### Meta-analysis: Effectiveness of Drugs for Preventing Contrast-induced Nephropathy

*Ann Intern Med* 2008;148:284-294

**Purpose:** To determine the effectiveness of N-acetylcysteine, theophylline, fenoldopam, dopamine, iloprost, statin, furosemide, or mannitol on preventing nephropathy.

**Study Selection:** Only randomized, controlled trials that used these agents in patients receiving iodinated contrast.

**Results:** In the 41 RCTs included N-acetylcysteine ( $\text{RR} = 0.62$  [0.44-0.88]) and Theophylline ( $\text{RR} = 0.49$  [0.23-1.06]) reduced the risk of nephropathy more than saline alone. Furosemide increased the risk ( $\text{RR} = 3.27$  [1.49-7.26]). Other agents did not affect risk of nephropathy.

**Conclusion:** N-acetylcysteine is more renoprotective than hydration alone.

## Analgesic Nephropathies

### 1. Vasomotor Acute Kidney Injury (AKI)

- normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
- NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
- more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
- clinically: develop prerenal azotemia within a few days of starting NSAID
- treatment: discontinue NSAID, dialysis rarely needed

### 2. Acute Interstitial Nephritis (AIN)

- fenoprofen (60%), ibuprofen, naproxen
- may be associated with minimal change glomerulopathy and nephrotic range proteinuria
- resolves eventually with discontinuation of NSAID, may require interval dialysis
- short term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

### 3. Chronic Interstitial Nephritis

- due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
- seen in patients who also have emotional stress, psychiatric symptoms and GI disturbance
- papillary necrosis
  - gross hematuria, flank pain, declining renal function
  - calyceal filling defect seen with IVP – “ring sign”
- increased risk of transitional cell carcinoma of renal pelvis
- good prognosis if discontinue analgesics

### 4. Acute Tubular Necrosis (ATN)

- can be caused by acetaminophen
  - incidence of renal dysfunction is related to the severity of acetaminophen ingestion
- vascular endothelial damage can also occur
- both direct toxicity and ischemia contribute to the tubular damage
- renal function spontaneously returns to baseline within 1-4 wk
- dialysis may be required during the acute episode of ingestion

### 5. Other Effects of NSAIDs

- sodium retention (2° to reduced GFR)
- hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
- excess water retention (due to elimination of ADH – antagonistic effect of prostaglandins)

## Systemic Disease with Renal Manifestation

### Diabetes

- diabetic nephropathy: presence of microalbuminuria or overt nephropathy (i.e. macroalbuminuria) in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 35-50% of patients with Type 1 DM will develop nephropathy, unknown percentage of Type 2
- at diagnosis up to 30% of patients with Type 2 DM have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once macroalbuminuria is established, renal function declines, 50% patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially Type 1 DM) and/or neuropathy (especially Type 2 DM)
- indication of possible nondiabetic cause of renal disease in patients with DM:
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of systemic disease
  - inappropriate time course; rapidly rising Cr, renal disease in a patient with short duration of DM
  - family history of nondiabetic renal disease (e.g. PCKD, Alport's)



DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD. The others are amyloidosis, HIV nephropathy, PCKD and multiple myeloma.



Abnormal Urine ACR Values from 2008 Canadian Diabetes Association CPG  
>2.0 mg/mmol in males  
>2.8 mg/mmol in females



ACEI can cause hyperkalemia. Therefore, be sure to watch serum K<sup>+</sup>, especially if patient has DM and renal insufficiency.

## DIABETIC RENAL COMPLICATIONS

### 1. Progressive Glomerulosclerosis

- classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
- more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix

**Table 13. Stages of Diabetic Progressive Glomerulosclerosis**

Stage 1	Stage 2	Stage 3	Stage 4
<ul style="list-style-type: none"> <li>• ↑ GFR (120-150%)</li> <li>– compensatory hyperfiltration</li> <li>• ± slightly increased mesangial matrix</li> </ul>	<ul style="list-style-type: none"> <li>• Detectable microalbuminuria (0-300 mg/24 h)</li> <li>• Albumin-Creatinine ratio (ACR) 2.0–20 mg/mmol in men (18-180 mg/d),</li> <li>• ACR 2.8-28 mg/mmol in women (25-250 mg/d)</li> <li>• ↑ mesangial matrix</li> </ul>	<ul style="list-style-type: none"> <li>• Macroalbuminuria (&gt;300 mg/24 h)</li> <li>• ACR in men &gt;20 mg/mmol, (&gt;180 mg/d)</li> <li>• ACR in women &gt;28 mg/mmol (&gt;250 mg/d)</li> <li>• Proteinuria (+ve urine dipstick)</li> <li>• Normal GFR</li> <li>• ↑↑↑ mesangial matrix</li> </ul>	<ul style="list-style-type: none"> <li>• ↑ proteinuria (&gt;500 mg/24 h)</li> <li>• ↓ GFR</li> <li>• &lt;20% glomerular filtration surface area present</li> <li>• Sclerosed glomeruli</li> </ul>

### 2. Accelerated Atherosclerosis

- common finding
- decreased GFR
- may increase Angiotensin II production resulting in increased BP
- increased risk of ATN secondary to contrast media

### 3. Autonomic Neuropathy

- affects bladder leading to functional obstruction and urinary retention
- residual urine promotes infection
- obstructive nephropathy

### 4. Papillary Necrosis

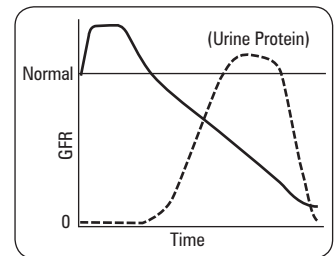
- Type 1 DM susceptible to ischemic necrosis of medullary papillae
- sloughed papillae may obstruct ureter
- can present as renal colic or with obstructive features ± hydronephrosis

## 2013 Canadian Diabetics Association Clinical Practice Guidelines on Chronic Kidney Disease in Diabetes

- screen for microalbuminuria with a random urine test for albumin to Cr ratio (ACR) and eGFR with a serum creatinine (e.g. using MDRD equation)
  - Type 1 DM: annually In post-pubertal individuals after 5 yr of diagnosis
  - Type 2 DM: at diagnosis, then annually
  - If eGFR >60 mL/min or ACR <2.0 mg/mmol: there is no CKD, re-screen in 1 yr
  - If urine ACR >20.0 mg/mmol: diagnose CKD.
  - If ACR <20.0 mg/mmol but >2.0 mg/mmol: order serum Cr for eGFR in 3 mo and 2 repeats of random urine ACRs over the next 3 mo. At 3 mo: If eGFR ≤60 mL/min or if >2/3 ACRs are >2.0 mg/mmol, diagnose CKD
  - if CKD diagnosed, ordered urine R+M and dipstick, if negative then diagnose CKD in Diabetes
  - with CKD in Diabetes: urine ACR and serum Cr (for eGFR) every 6 mo
  - delay screening if transient cause of albuminuria or low eGFR
- evaluate for other causes of proteinuria, rule out nondiabetic renal disease
- avoid unnecessary potential nephrotoxins (NSAIDs, aminoglycosides, dye studies)

## Priorities in the Management of Patients with DM

1. vascular protection for all patients with diabetes
  - ACEI, antiplatelet therapy (as indicated)
  - BP control, glycemic control, lifestyle modification, lipid control
2. optimization of BP in patients who are hypertensive
  - treat according to hypertension guidelines
3. renal protection for DM patients with nephropathy (even in absence of HTN)
  - Type 1 DM: ACEI
  - Type 2 DM: CrCl >60 mL/min: ACEI or ARB – CrCl <60 mL/min: ARB
  - 2<sup>nd</sup> line agents: nondihydropyridine calcium channel blockers (diltiazem, verapamil)
  - ACEI and ARB can be safely used together if needed for control of significant proteinuria (monitor for hyperkalemia and acute rise in Cr)
- check serum Cr and K<sup>+</sup> levels within 1 wk of initiating ACEI or ARB and at time of acute illness
- serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
- if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2<sup>nd</sup> line agent
- consider holding ACEI, ARB and/or diuretic with acute illness and in women before becoming pregnant
- consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive kidney function loss, unable to achieve BP targets or unable to stay on ACEI or ARB



**Figure 16. GFR and urine protein over time in diabetes**



### Renoprotective Effect of Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes.

NEJM 2001;345:851-860

**Study:** Multicentre, RCT, mean follow-up of 2.6 yr.  
**Patients:** 806 patients (mean age 70) with T2DM, HTN, and nephropathy (24hr proteinuria >900 mg, serum Creatinine (Cr) 88(Male)/106(Female)-265 µmol/L)

**Intervention:** BP control with irbesartan vs. amlodipine vs. placebo, with use of adjuncts (not including ACEs, ARBs, or CCI) as needed.

**Outcomes:** Primary composite endpoint included doubling of serum Cr, ESRD, or death. Secondary composite endpoint included morbidity and mortality from CVD causes.

**Results:** BP control was similar in all three arms. Irbesartan had a relative risk reduction of 20% vs. placebo and 23% vs. amlodipine for the primary end point. The irbesartan group had a 33% risk reduction vs. placebo and 37% reduction vs. amlodipine for risk of doubling serum Cr. Serum Cr increased more slowly in the Irbesartan group versus placebo or amlodipine. No difference in absolute mortality or secondary end point.

**Conclusion:** Irbesartan conferred significant renoprotective benefits in patients with type 2 diabetes and nephropathy, independent of blood pressure lowering effects.



### Renal Outcomes with Telmisartan, Ramipril, or Both in People at High Vascular Risk (ONTARGET Study)

Lancet 2008;372:547-553

**Study:** Prospective, multicentre, double-blind, randomized controlled trial.

**Participants:** 25,620 patients with median follow-up of 56 mo.

**Intervention:** Patients received either ramipril (10 mg/d; N=8576), telmisartan (80 mg/d; N=8542) or a combination of both drugs (N=8502).

**Primary Outcome:** Composite of dialysis, doubling of creatinine level, and death.

**Results:** The number of outcome events was similar for telmisartan (n=1147) and ramipril (1150; HR 1.00, CI 0.92-1.09), but was increased with combination therapy (1233; HR 1.09, 1.01-1.18, p=0.037). The need for dialysis or doubling of serum creatinine, was similar with telmisartan (189) and ramipril (174; HR 1.09, 0.89-1.34) and more frequent with combination therapy (212; HR 1.24, 1.01-1.51, p=0.038). Estimated GFR declined least with ramipril compared with telmisartan or combination therapy (p<0.001). The increase in urinary albumin excretion was less with telmisartan (p=0.004) and combination therapy (p=0.001) than with ramipril.

**Conclusion:** Renal outcomes were similar in both telmisartan and ramipril monotherapy. Combination therapy reduced proteinuria to a greater extent than monotherapy, but was associated with poorer renal outcomes.

## Scleroderma

- 50% of scleroderma patients have renal involvement (mild proteinuria, high Cr, HTN)
- histology: media thickened, "onion skin" hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
- 10-15% scleroderma patients have a "scleroderma renal crisis" (occurs in first few years of disease): malignant HTN, ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- renal involvement usually occurs early in the course of illness
- treatment: BP control with ACEI slows progression of renal disease

## Multiple Myeloma

- see [Hematology](#), H47
- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms:
  - hypercalcemia
  - light chain cast nephropathy (LCCN, see below) or "myeloma kidney"
  - hyperuricemia
  - infection
  - secondary amyloidosis
  - monoclonal Ig deposition disease (MIDD)
  - diffuse tubular obstruction
- LCCN
  - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
  - proteinuria and renal insufficiency, can progress rapidly to kidney failure
- MIDD
  - deposits of monoclonal Ig in kidney, liver, heart and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

## Malignancy

- cancer can have many different renal manifestations
- kidney transplantation cannot be performed unless malignancy is cured
  - solid tumours: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
  - renal cell carcinoma
  - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumours/mets: post-renal failure secondary to obstruction
  - 2° amyloidosis
  - radiotherapy (radiation nephritis)

## Hypertension (HTN)

- HTN occurs in about 20% of population
- etiology classified as primary ("essential"; makes up 90% of cases) or secondary
- primary: hypertension due to other factors that cause renal disease (hypertensive nephrosclerosis) or worsen pre-existing renal disease
- secondary: diseases of renal parenchyma or renal vasculature that cause hypertension



### Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 DM and Nephropathy

NEJM 2001;345:861-869

**Study:** Randomized, double-blind, placebo-controlled trial with mean follow-up of 3.4 yr.

**Patients:** 1513 patients (mean age 60, 63% male, multi-ethnicity) with NIDDM and nephropathy (urinary albumin:Cr  $\geq 300$  and serum Cr 115-265  $\mu\text{mol/L}$ ) on conventional antihypertensives (CCB, diuretics,  $\beta$ -blockers, centrally acting agents).

**Intervention:** Losartan 50 mg PO OD (could be doubled after 4 wk) vs. placebo.

**Outcomes:** Primary endpoints included doubling of serum Cr, ESRD, or death. Secondary endpoints included morbidity and mortality from CVD causes.

**Results:** Losartan reduced incidence of doubling of serum Cr (RR 25%) and ESRD (RR 28%), but had no effect on risk of death. Benefit exceeded that attributable to BP changes alone. Secondary endpoints were similar, although rate of hospitalization for heart failure was significantly lower with losartan (RR 32%).

**Conclusion:** Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and was generally well tolerated.



### Protein Restriction for Diabetic Renal Disease

Cochrane DB Syst Rev 2007;4:CD002181

**Purpose:** To review the effects of dietary protein restriction on the progression of diabetic nephropathy.

**Study Selection:** Randomized controlled trials (RCTs) and before and after studies of the effects of restricted protein diet on renal function in subjects with diabetes. 12 studies were reviewed.

**Results:** The risk of end-stage renal disease or death was lower in patients on low-protein diet. In patients with Type 1 diabetes no effect on GFR was noted in the low-protein diet group.



### Long-term Outcomes of Scleroderma Renal Crisis

Ann Intern Med 2000;133:600-603

**Study:** Prospective observational cohort study with follow up of 5-10 yr.

**Patients:** 145 patients with scleroderma renal crisis who received ACE inhibitors and 662 patients with scleroderma who did not have renal crisis.

**Primary Outcome:** The need for dialysis and early death among patients with renal crisis.

**Results:** Sixty-one percent of patients with renal crisis had good outcomes (55 had no dialysis and 34 received temporary dialysis); only 4 of these patients progressed to chronic renal failure and permanent dialysis. Greater than 50% of the patients who initially required dialysis discontinued it 3 to 18 mo later. Permanent dialysis or early death occurred in 39% of the patients.

**Conclusion:** Renal crisis can be managed when hypertension is aggressively controlled with ACE inhibitors.



### Features of Multiple Myeloma

#### CARLI

Calcium (elevated)

Anemia

Renal Failure

Lytic Bone Lesions

Infections



## Hypertensive Nephrosclerosis

Table 14. Chronic vs. Malignant Nephrosclerosis

	Chronic Nephrosclerosis	Malignant Nephrosclerosis
<b>Histology</b>	Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles	Fibrinoid necrosis of arterioles, disruption of vascular endothelium
<b>Clinical Picture</b>	African American, underlying chronic kidney disease, chronic hypertensive disease	Acute elevation in BP (dBP >120 mmHg) HTN encephalopathy
<b>Urinalysis</b>	Mild proteinuria, normal urine sediment	Proteinuria and hematuria (RBC casts)
<b>Therapy</b>	Blood pressure control, (target <140/90) with frequent follow-up	Lower dBP to 100-110 mmHg within 6-24 h More aggressive treatment can cause ischemic event Identify and treat underlying cause of HTN
<b>Prognosis</b>	Can progress to renal failure despite patient adherence	Lower survival if renal insufficiency develops

## Renovascular Hypertension

- see *Vascular Diseases of the Kidney*, NP17

## Renal Parenchymal Hypertension

- HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include
  - excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective sodium excretion with fluid overload

### Investigations

- as well as investigations for renovascular HTN, additional tests may include
  - 24-h urinary estimations of Cr clearance and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy

### Treatment

- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na<sup>+</sup> restriction (88 mmol/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor K<sup>+</sup> and Cr) if there is significant proteinuria (>300 mg/d)

## Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population over 50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive) and acquired cystic kidney disease (in chronic hemodialysis patients)



Hypercalcemia complicates many cancers and can cause multiple kinds of renal disorders (renal vasoconstriction with reduced OTR; salt-wasting with volume depletion; risk of calcium kidney stones).

## Adult Polycystic Kidney Disease

- autosomal dominant; at least 2 genes: *PKD1* (chr 16p) and *PKD2* (chr 4q)
- *PKD1* (1:400), *PKD2* (1:1000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant polycystin gene but accumulate a series of second 'somatic hits' precipitating the condition
- *PKD1* encodes a protein that is responsible for cell-cell and cell-matrix interaction and sensing fluid flow by associating with cilia
- *PKD2* encodes a protein that is a Ca<sup>2+</sup> permeable nonselective cation channel that associates with cilia and is thought to control intracellular Ca<sup>2+</sup> in response to flow
- defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth
- extrarenal manifestations: most common; multiple asymptomatic hepatic cysts (33%), cerebral aneurysm (10%), diverticulosis and mitral valve prolapse (25%)
- polycystic liver disease rarely causes liver failure
- less common: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta



**Signs and Symptoms**

- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain
- hematuria (microscopic frequently initial sign, gross)
- nocturia (urinary concentrating defect)
- rarely extra-renal presentation (e.g. ruptured berry aneurysm, diverticulitis)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- $\pm$  palpable kidneys

**External Manifestations of PKD**

- Hepatic cysts
- Cerebral aneurysms
- Diverticulosis
- Mitral valve prolapse

**Common Complications**

- urinary tract and cyst infections, HTN, CRF, nephrolithiasis (5-15%), flank and chronic back pain

**Clinical Course**

- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10 times normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

**Investigations**

- radiographic diagnosis: best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- gene linkage analysis for PKD1 for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)

**Treatment**

- goal: to preserve renal function by prevention and treatment of complications
- educate patient and family about disease, its manifestations and inheritance pattern
- genetic counselling: transmission rate 50% from affected parent
- prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
- TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
- adequate hydration to prevent stone formation
- avoid contact sports due to greater risk of injury to enlarged kidneys
- screen for cerebral aneurysms if family history of aneurysmal hemorrhages
- monitor blood pressure and treat hypertension with ACEI
- dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
- may require nephrectomy to create room for renal transplant

## Medullary Sponge Kidney

- common, autosomal dominant, usually diagnosed in 4th-5th decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney
- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP, characteristic radial pattern ("bouquet of flowers"), "swiss cheese" appearance on morphology
- treat UTIs and stone formation as indicated
- does not result in renal failure

## Autosomal Recessive Polycystic Kidney Disease

- 1:20,000 incidence
- prenatal diagnosis by enlarged kidneys
- perinatal death from respiratory failure
- patients who survive perinatal period develop CHF, HTN, chronic kidney disease
- treated with kidney and/or liver transplant

# Acute Kidney Injury (AKI)

## Definition

- abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
- formerly known as Acute Renal Failure (ARF)

## Clinical Features

- azotemia (increased BUN, Cr)
- abnormal urine volume (anuria, oliguria, polyuria)

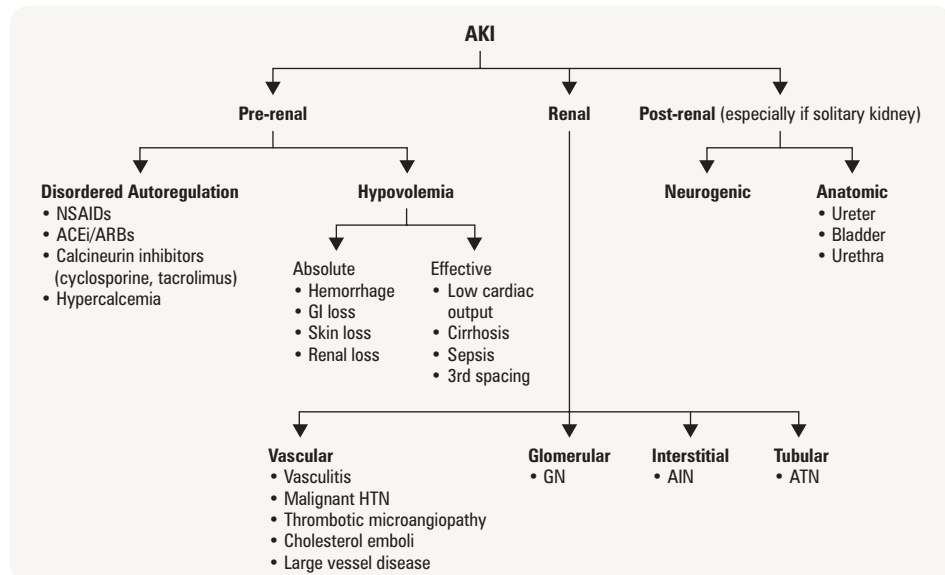


Figure 17. Approach to acute kidney injury

## Approach to AKI

### Investigations

- blood: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr),  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$
- urine volume, C&S, R&M: sediment, casts, crystals
- urinary indices: electrolytes, osmolality
- Foley catheterization (rule out bladder outlet obstruction)
- fluid challenge (i.e. fluid bolus to rule out most pre-renal causes)
- imaging: abdo U/S (assess kidney size, hydronephrosis, post-renal obstruction)
- indications for renal biopsy
  - diagnosis is not certain
  - prerenal azotemia or ATN is unlikely
  - oliguria persists >4 wk

### Treatment

#### 1. preliminary measures

- pre-renal
  - ♦ correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEi/ARB (gently rehydrate when needed, i.e. CHF)
- renal
  - ♦ address reversible renal causes: d/c nephrotoxic drugs, treat infection, and optimize electrolytes
- post-renal
  - ♦ consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
  - ♦ treat with Foley catheter, indwelling bladder catheter, nephrostomy, stenting

#### 2. treat complications

- fluid overload
  - ♦ NaCl restriction
  - ♦ high dose loop diuretics
- hyperkalemia (refer to *Approach to Hyperkalemia*, NP13)



The 2 most common causes of acute kidney injury in hospitalized patients are prerenal azotemia and acute tubular necrosis. Remember that prerenal failure can lead to ATN.



#### Clues to Pre-Renal Etiology

- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
- Increased [urea] >> Increased [Cr]
- Urine  $[\text{Na}^+]$  <10-20 mmol/L
- Urine osmolality >500 mOsm/kg
- Fractional excretion of  $\text{Na}^+$  <1%

#### Clues to Renal Etiology

- Appropriate clinical context
- Urinalysis positive for casts:
  - Pigmented granular – ATN
  - WBC – AIN
  - RBC – GN

#### Clues to Post-Renal Etiology

- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis



#### Differentiating Pre-renal from ATN

	Pre-renal	ATN
Urinalysis	Normal	RBC, pigmented granular casts
Urine $[\text{Na}^+]$	<20	>40 mEq/L
Urine $[\text{Na}^+]/[\text{Cr}]$	<20	>40
Urine osmolality	>500	<350 mOsm/kgH <sub>2</sub> O
FeNa	<1	>1%



#### Drugs Implicated in Pre-Renal Azotemia

- Anti-hypertensives
- Diuretics
- NSAIDs
- ACEi/ARBs

- adjust dosages of medications cleared by kidney (e.g. amiodarone, digoxin, cyclosporin, tacrolimus, some antibiotics and chemotherapeutic agents)
  - dialysis
3. definitive therapy depends on etiology
- note: renal transplant is not a therapy for AKI

### Prognosis

- high morbidity and mortality in patients with sustained AKI and multi-organ failure

## Chronic Kidney Disease (CKD)

### Definition

- progressive and irreversible loss of kidney function
- abnormal markers (Cr, urea)
  - GFR <60 mL/min for >3 mo or
  - kidney pathology seen on biopsy or
  - decreased renal size on U/S (kidneys <9 cm)
- clinical features of chronic kidney disease
  - volume overload and hypertension
  - electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
  - uremia

**Table 15. Stages of Chronic Kidney Disease (KDIGO, 2013)**

		Persistent Albuminuria Categories			
		GFR (mL/min/1.73m <sup>2</sup> )	A1 <30 mg/g <3 mg/mmole	A2 30-300 mg/g 3-30 mg/mmole	A3 >300 mg/g >30 mg/mmole
GFR categories (mL/min/1.73m <sup>2</sup> )	G1	≥90	1 if CKD	1	2
	G2	60-89	1 if CKD	1	2
	G3a	45-59	1	2	3
	G3b	30-44	2	3	3
	G4	15-29	3	3	4+
	G5	<15 (kidney failure)	4+	4+	4+

The numbers in the boxes are a reflection of the risk of progression and are a guide to the frequency of monitoring/year

"D" is added to G5 for patients requiring dialysis

Classification is based on cause, GFR and amount of albuminuria

Rate of progression and risk of complications are determined by the cause of CKD



### Incidence of Etiologies of Chronic Kidney Disease (CKD)

Diabetes	42.9%
Hypertension	26.4%
Glomerulonephritis	9.9%
Other/Unknown	7.7%
Interstitial nephritis/	
Pyelonephritis	4.0%
Cystic/Hereditary/Congenital	3.1%
Secondary GN/Vasculitis	2.4%



### Management of Complications of CKD

#### NEPHRON

- N** – Low-nitrogen diet
- E** – Electrolytes: monitor K<sup>+</sup>
- P** – pH: metabolic acidosis
- H** – Hypertension
- R** – RBCs: manage anemia with erythropoietin
- O** – Osteodystrophy: give calcium between meals (to increase Ca<sup>2+</sup>) and calcium with meals (to bind and decrease PO<sub>4</sub><sup>3-</sup>)
- N** – Nephrotoxins: avoid nephrotoxic drugs (ASA, gentamicin) and adjust doses of renally excreted medications



### Renin Angiotensin System Blockade and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Proteinuria: A Meta-analysis

*Am Heart J* 2008;155:791-805

**Purpose:** To evaluate the role of renin angiotensin system (RAS) blockade in improving cardiovascular CV outcomes in patients with chronic kidney disease (CKD).

**Study Selection:** Randomized controlled trials that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (ACEI/ARB). Renin angiotensin system blockade-based therapy was compared with placebo and control (β-blocker, calcium-channel blockers and other antihypertensive-based therapy) therapy in the study.

**Results:** Twenty-five trials (N = 45758) were included. Compared to placebo, RAS blockade reduced the risk of heart failure in patients with diabetic nephropathy. In patients with non-diabetic CKD, RAS blockade decreased CV outcome compared to control therapy.

**Conclusions:** RAS blockade reduced CV outcomes in diabetic nephropathy as well as non-diabetic CKD.

## Management of Chronic Kidney Disease

- diet
  - protein restriction with adequate caloric intake limits endogenous protein catabolism
  - K<sup>+</sup> restriction (40 mmol/d)
  - Na<sup>+</sup> and water restriction
  - PO<sub>4</sub><sup>3-</sup> restriction (1 g/d)
  - avoid extra-dietary Mg<sup>2+</sup> (i.e. antacids)
- medical
  - treatment of secondary hyperparathyroidism
  - calcium supplements (e.g. TUMS®) treats hypocalcemia when given between meals and binds phosphate when given with meals
  - consider calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic
  - sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
  - vitamin D analogues are being introduced in the near future
  - cinacalcet for hyperparathyroidism (sensitizes parathyroid to Ca<sup>2+</sup>, decreasing PTH)
  - sodium bicarbonate for metabolic acidosis
  - erythropoietin injections (Hct <30%) for anemia; target Hct 33-36%
  - DDAVP for prolonged bleeding time if patient has clinical bleeding or invasive procedures
  - ACEI for hypertension (target 130/80 or less), loop diuretics when GFR <25 mL/min
  - statins for dyslipidemia
  - adjust dosages for renally excreted medications (avoid nephrotoxic medications)
- dialysis (hemodialysis, peritoneal dialysis)
- renal transplantation

### Prevention of Progression

- as above
- control of hypertension, diabetes, cardiovascular risk factors (e.g. smoking cessation)
- avoid nephrotoxins
- address reversible causes of AKI

## Renal Failure

### Presentation of Renal Failure

#### 1. Volume Overload

- due to increase in total body  $\text{Na}^+$  content
- signs: weight gain, HTN, pulmonary or peripheral edema

#### 2. Electrolyte Abnormalities

- high
  - $\text{K}^+$  (decreased renal excretion, increased tissue breakdown)
  - $\text{PO}_4^{3-}$  (decreased renal excretion, increased tissue breakdown)
  - $\text{Ca}^{2+}$  (rare; happens during recovery phase after rhabdomyolysis-induced acute kidney injury or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
  - uric acid
- low
  - $\text{Na}^+$  (failure to excrete excessive water intake)
  - $\text{Ca}^{2+}$  (decreased Vit D activation, hyperphosphatemia, hypoalbuminemia)
  - $\text{HCO}_3^-$  (especially with sepsis or severe heart failure)

#### 3. Uremic Syndrome

- manifestations result from retention of urea and other metabolites as well as hormone deficiencies

### Signs and Symptoms of Renal Failure

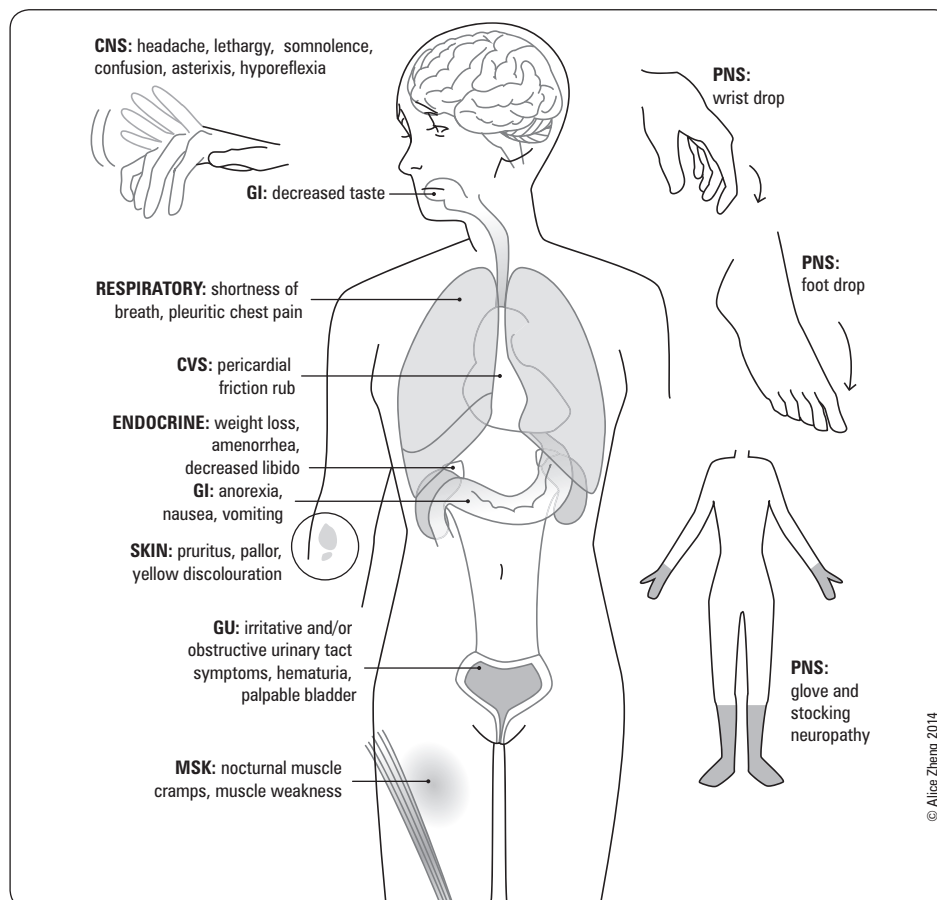


Figure 18. Signs and symptoms of renal failure

### Complications

- CNS: decreased LOC, stupor, seizure
- CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- GI: peptic ulcer disease, gastroduodenitis, AVM
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
- endocrine:
  - decreased testosterone, estrogen, progesterone
  - increased FSH, LH
- metabolic:
  - renal osteodystrophy: secondary increased PTH due to decreased  $\text{Ca}^{2+}$ , high  $\text{PO}_4^{3-}$  and low active vitamin D
    - ♦ osteitis fibrosa cystica
  - hypertriglyceridemia, accelerated atherogenesis
  - decreased insulin requirements, increased insulin resistance
- dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular  $\text{Ca}^{2+}$  deposition)

## Renal Replacement Therapy

### Dialysis

#### Indications for Dialysis in Chronic Renal Failure

Table 16. Indications for Dialysis

Absolute Indications	Relative Indications
<ul style="list-style-type: none"> <li>• Volume overload*</li> <li>• Hyperkalemia*</li> <li>• Severe metabolic acidosis*</li> <li>• Neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures)</li> <li>• Uremic pericarditis</li> <li>• Refractory accelerated hypertension</li> <li>• Clinically significant bleeding diathesis</li> <li>• Persistent severe nausea and vomiting</li> <li>• Plasma Cr &gt; 1060 <math>\mu\text{mol/L}</math> (12 mg/dL) or Urea &gt; 36 mmol/L (100 mg/dL; clinical picture also important)</li> </ul>	<ul style="list-style-type: none"> <li>• Anorexia</li> <li>• Decreased cognitive functioning</li> <li>• Profound fatigue and weakness</li> <li>• Severe anemia unresponsive to erythropoietin</li> <li>• Persistent severe pruritus</li> <li>• Restless leg syndrome</li> </ul>

\*Unresponsive to medications

- **hemodialysis:** blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  - available as intermittent (e.g. three times per week), continuous (CVVHD) or sustained low efficiency (SLED)
  - can be delivered at home or in-centre, nocturnal
  - vascular access can be achieved through a central line, an artificial graft or an arterio-venous fistula
- patients with chronic kidney disease should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350  $\mu\text{mol/L}$  (>4.0 mg/dL), or within 1 yr of an anticipated need
- **peritoneal dialysis:** peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  - available as continuous ambulatory (CAPD; four exchanges per day) or cyclic (CCPD; machine carries out exchanges overnight)
- refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)



#### Indications for Dialysis

##### HAVE PEE or AE IOU

Hyperkalemia (refractory)  
Acidosis (refractory)  
Volume overload (refractory)  
Elevated urea (>35-50 mM)  
Pericarditis  
Encephalopathy  
Edema (pulmonary)

or

Acidosis  
Electrolyte imbalance ( $\text{K}^+$ )  
Intoxication  
Overload  
Uremic encephalopathy, pericarditis, urea > 35-50 mM



#### How to Write Dialysis Orders (MUST BE INDIVIDUALIZED)

- Filter Type (e.g. F80)
- Length (e.g. 4h 3 times/wk or 2h daily)
- Q Blood Flow (max 500 cc/min)
- Ultrafiltration (e.g. 2 L or to target dry weight)
- $\text{Na}^+$  140 (can be adjusted by starting at 155 and "ramping" down to minimize cramping)
- $\text{K}^+$  [based on serum ( $\text{K}^+$ )]  
 Serum  $\text{K}^+$     Dialysate  
 4-6            1.5  
 3.5-4        2.5  
 <3.5        3.5
- $\text{Ca}^{2+}$  1.25
- $\text{HCO}_3^-$  40
- Heparin [none, tight (500 U/h) or full (1000 U/h)]
- IV fluid to support BP (e.g. N/S)

Table 17. Peritoneal Dialysis vs. Hemodialysis

	Peritoneal Dialysis	Hemodialysis
<b>Rate</b>	Slow	Fast
<b>Location</b>	Home	Hospital (usually)
<b>Ultrafiltration</b>	Osmotic pressure via dextrose dialysate	Hydrostatic pressure
<b>Solute Removal</b>	Concentration gradient and convection	Concentration gradient and convection
<b>Membrane</b>	Peritoneum	Semi-permeable artificial membrane
<b>Method</b>	Indwelling catheter in peritoneal cavity	Line from vessel to artificial kidney
<b>Complications</b>	Infection at catheter site Bacterial peritonitis Metabolic effects of glucose Difficult to achieve adequate clearance in patients with large body mass	Vascular access (clots, collapse) Bacteremia Bleeding due to heparin Hemodynamic stress of extracorporeal circuit Disequilibrium syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/water flux over short time)
<b>Preferred When</b>	Young, high functioning, residual renal function Success depends on presence of residual renal function	Bed-bound, co-morbidities, no renal function Residual renal function not as important

**When to Initiate Dialysis**

CrCl &lt; 20 mL/min

- Educate patient regarding dialysis; if not a candidate for peritoneal dialysis, make arrangements for AV fistula

CrCl &lt; 15 mL/min

- Weigh risk and benefits for initiating dialysis

CrCl &lt; 10 mL/min

- Dialysis should be initiated

**NOTE**

- Cockcroft-Gault equation (or Modification of Diet in Renal Disease equation) should be used to measure kidney function
- Monitor for uremic complications
- Significant benefits in quality of life can occur if dialysis started before CrCl < 15 mL/min
- It is unclear whether patients who start dialysis early have increased survival
- A preemptive transplant can be considered if patient is stable, in order to avoid dialysis

From: National Kidney Foundation/Kidney Disease Outcome. Quality Initiative

**Commonly Used Immunosuppressive Drugs****Calcineurin inhibitors**

- Cyclosporine
- Tacrolimus

**Antiproliferative medications**

- Mycophenolate Mofetil
- Azathioprine

**Other agents**

- Sirolimus
- Prednisone

**Anti-lymphocyte antibodies**

- Thymoglobulin
- Basiliximab

**Survival Among Nocturnal Home Haemodialysis Patients Compared to Kidney Transplant Recipients**

Nephrol Dial Transplant 2009;24:2915-2919

**Study:** Retrospective, matched cohort with 4-5 yr average follow up.

**Population:** 177 nocturnal home dialysis (NHD) patients (mean age 46, 68% white) were matched to 533 deceased donor transplant (DTX) patients and 533 live donor (LTX) transplant patients (1:3:3 ratio).

**Intervention:** Nocturnal home dialysis versus live or deceased donor transplant.

**Outcome:** Primary outcome was all cause mortality  
**Results:** No significant difference in survival or hazard ratio between NHD and DTX. Significant survival benefit for patients undergoing LTX versus NHD. Significant mortality hazard ratio reduction with LTX (0.51) with no difference in hazard ratio for DTX versus NHD reference.

**Conclusion:** NHD has comparable mortality to DTX, but is inferior to LTX.

## Renal Transplantation

- preferred modality of RRT, best way to reverse uremic signs and symptoms
- provides maximum replacement of GFR
- only therapy shown to improve survival in patients with ESRD
- native kidneys usually left in situ
- 2 types: deceased donor, living donor (related or unrelated)
- kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- 1 yr renal allograft survival rates ≥90%

**Complications**

- leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
- #1 cause of mortality in transplanted patients is cardiovascular disease
- immunosuppressant drug therapy: side effects include infections, malignancy (skin, Kaposi's sarcoma, post-transplant lymphoproliferative disorder)
- acute rejection: graft site tenderness, rise in Cr, oliguria, ± fever, although symptoms are uncommon
- de novo glomerulonephritis (usually membranous)
- new-onset diabetes mellitus (often due to prednisone use)
- cyclosporine or tacrolimus nephropathy (refer to *Small Vessel Disease*, NP18)
- chronic allograft nephropathy
  - early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
  - immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset diabetes)
  - transplant glomerulopathy from antibody injury causes nephrotic proteinuria
- CMV (cytomegalovirus) infection and other opportunistic infections usually occur between 1 and 6 mo post-transplant
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss



## Common Medications

Table 18. Common Medications in Nephrology

Classification	Examples	Site of Action	Mechanism of Action (Secondary Effect)	Indication	Dosing	Adverse Effects
<b>Loop Diuretics</b>	furosemide (Lasix®) bumetanide (Bumex®/Buinex®) ethacrynate (Edecrin®) torsemide (Demadex®)	Thick ascending of Loop of Henle	↓ Na <sup>+</sup> /K <sup>+</sup> /2Cl <sup>-</sup> transport ± renal and peripheral vasodilatory effects (K <sup>+</sup> loss; ↑ H <sup>+</sup> secretion; ↑ Ca <sup>2+</sup> excretion)	Management of edema secondary to CHF, nephrotic syndrome, cirrhotic ascites; ↑ free water clearance (e.g. in SIADH-induced hyponatremia), ↓ BP (less effective due to short action)	furosemide: edema – 20-80 mg IV/IM/PO q6-8h (max 600 mg/d) until desired response HTN – 20-80 mg/d PO OD/bid dosing	Allergy in sulfa-sensitive individuals Electrolyte abnormalities; hypokalemia, hyponatremia, hypocalcemia, hypercalciuria (with stone formation) Volume depletion with metabolic alkalosis Precipitates gouty attacks
<b>Thiazide Diuretics</b>	hydrochlorothiazide (HCTZ) chlorothiazide (Diuril®) indapamide (Lozo®, Lozide®) metolazone (Zaroxolyn®) chlorthalidone (Hygroton®)	Distal convoluted tubule	Inhibit Na <sup>+</sup> /Cl <sup>-</sup> transporter (K <sup>+</sup> loss; ↑ H <sup>+</sup> secretion; ↓ Ca <sup>2+</sup> excretion)	1st line for essential HTN Treatment of edema Idiopathic hypercalciuria and stones Diabetes Insipidus (nephrogenic)	HCTZ: edema – 25-100 mg PO OD HTN – 12.5-25 PO OD (max 50 mg/d) nephrolithiasis/hypercalciuria – 25-100 mg OD	Hypokalemia Increased serum urate levels Precipitates gouty attacks, hypercalcemia Elevated lipids Glucose intolerance
<b>Potassium-Sparing Diuretics</b>	spironolactone (Aldactone®) triarterene (Dyrenium®) amiloride (Midamor®)	Cortical collecting duct (↓ Na <sup>+</sup> reabsorption)	Aldosterone antagonist Closes apical Na <sup>+</sup> channels directly	Reduces K <sup>+</sup> loss caused by other diuretics Edema/hypervolemia Severe CHF, ascites (spironolactone), cystic fibrosis (amiloride ↓ viscosity of secretions)	spironolactone: 25-200 mg/d OD/bid dosing HTN: 50-200 mg/d OD/bid dosing Hyperaldosteronism – 100-400 mg/d OD/bid dosing amiloride: edema/HTN: 5-10 mg PO OD	Hyperkalemia (caution with ACE inhibitor) Triarterene can be nephrotoxic (rare) Nephrolithiasis Gynecomastia (estrogenic effect of spironolactone)
<b>Combination Agents</b>	Dyazide® (triarterene + HCTZ) Aldactazide® (spironolactone + HCTZ) Moduretic® (amiloride + HCTZ) Vaseretic® (enalapril + HCTZ) Zestoretic® (lisinopril + HCTZ)		Combine ACE-inhibitor with thiazide for synergistic effect	Combine K <sup>+</sup> -sparing drug with thiazide to reduce hypokalemia		
<b>Osmotic Diuretics</b>	mannitol (Osmitol®) glycerol urea	Renal tubules (proximal and collecting duct)	Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate – inhibits reabsorption of water and ↑ urinary excretion of toxic materials	To ↓ intracranial or intraocular pressure Mobilization of excess fluid in renal failure or edematous states	mannitol: ↓ ICP: 0.25-2 g/kg IV over 30-60 min	Transient volume expansion Electrolyte abnormalities (↓/↑ Na <sup>+</sup> , ↓/↑ K <sup>+</sup> )
<b>ACEI</b>	ramipril (Altace®) enalapril (Vasotec®) lisinopril (Prinivil®) trandolapril (Mavik®) captopril (Capoten®)	Lungs Tissues diffusely	Prevents angiotensin II vasoconstricting vascular smooth muscle → net vasodilation → ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na <sup>+</sup> and H <sub>2</sub> O excretion → ↓ BP Reduces fibrosis and atherogenesis	HTN Cardioprotective effects (see <a href="#">Cardiology</a> ) Renoprotective effects	ramipril: HTN – 2.5-20 mg PO OD/bid dosing renoprotective use – 10 mg PO OD  trandolapril: HTN – 1-4 mg PO OD	Cough Asthma Hyperkalemia Angioedema Agranulocytosis (captopril) Acute kidney injury Teratogenic
<b>ARB</b>	losartan (Cozaar®) candesartan (Atacand®) irbesartan (Avapro®) valsartan (Diovan®) telmisartan (Micardis®) eprosartan (Teveten®) olmesartan (Olmetec®)	Vascular smooth muscle, adrenal cortex, proximal tubules	Competitive inhibitor at the angiotensin II receptor: prevents angiotensin II vasoconstricting action on vascular smooth muscle → ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na <sup>+</sup> and H <sub>2</sub> O excretion	HTN Cardioprotective effects (see <a href="#">Cardiology</a> ) Renoprotective effects	HTN: losartan 25-100 mg PO OD candesartan 8-32 mg PO OD irbesartan 150-300 mg PO OD valsartan 80-320 mg PO OD telmisartan 20-80 mg PO OD eprosartan 400-800 mg PO OD olmesartan 20-40 mg PO OD	Hyperkalemia Caution – reduce dose in hepatic impairment Acute kidney injury Teratogenic
<b>Renin Antagonists</b>	aliskiren (Rasilez®)	Direct renin antagonist	Inhibits renin production and activity Cardioprotective and renoprotective abilities being evaluated	HTN	aliskiren 150-300 mg PO OD	Hyperkalemia

## Landmark Nephrology Trials

Trial	Reference	Results
4D	<i>NEJM</i> 2005; 353:238-48	Patients with type 2 DM receiving maintenance hemodialysis were randomized to 20 mg of atorvastatin per day or matching placebo. No difference in composite index of death from cardiac causes, nonfatal myocardial infarction, and stroke
AASK	<i>JAMA</i> 2001; 285:2719-28	Ramipril, compared with amlodipine, slows progression of hypertensive renal disease and proteinuria and may benefit patients without proteinuria as well.
ACEI and Diabetic	<i>NEJM</i> 1993; 329:1456-62	Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood-pressure control alone
ALTITUDE	Early Termination (Unpublished Results; protocol – <i>NDT</i> 2009; 24:1663-71)	Combining Aliskiren with ACEI or ARB in high-risk patients with type 2 diabetes leads to increased incidence of nonfatal stroke, hyperkalemia and hypotension
ASTRAL	<i>NEJM</i> 2009; 361:1953-62	Renal artery revascularization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality and carries significant operative risks
AURORA	<i>NEJM</i> 2009; 360:1395-407	Patients receiving maintenance hemodialysis randomized to rosuvastatin 10 mg daily or placebo. Rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke
BENEDICT	<i>NEJM</i> 2004; 351:1941-51	Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 diabetes and hypertension with normoalbuminuria
CHOIR	<i>NEJM</i> 2006; 355:2085-98	Patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g/dL or 11.3 g/dL. The higher target group had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), or stroke
CREATE	<i>NEJM</i> 2006; 355:2071-84	Patients with CKD (15-35 mL/min) and mild to moderate anemia (11-12.5 g/dL) were randomized to normal (13-15 g/dL) or sub-normal (10.5-11.5 g/dL) hemoglobin levels. Early and complete correction of hemoglobin did not reduce the risk of cardiovascular events
DETAIL	<i>NEJM</i> 2004; 351:1952-61	The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 diabetes with mild to moderate hypertension and early nephropathy
ELITE-SYMPHONY	<i>NEJM</i> 2007; 357:2562-75	Daclizumab induction, MMF, steroids and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNi regimens
FHN	<i>NEJM</i> 2010;363:2287-300	Patients were randomized to dialysis 6x/wk (frequent) or 3x/wk (conventional). Frequent hemodialysis was associated with improvement in composite outcomes of death or change in left ventricular mass and death or change in a physical-health composite score. Frequent hemodialysis caused more frequent interventions related to vascular access
HEMO	<i>NEJM</i> 2002; 347:2010-19	Use of high dose dialysis or high flux membranes versus standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes. Possible benefit in cardiac-related outcomes with high flux membranes
IDEAL	<i>NEJM</i> 2010; 363:609-19	Patients with progressive CKD and GFR between 10 and 15 mL/min randomized to initiate dialysis at GFR of 10-14 mL/min (early) or 5-7 mL/min (late). Early initiation of dialysis in patients with stage V chronic kidney disease was not associated with an improvement in survival or clinical outcomes
IDNT	<i>NEJM</i> 2001; 345:851-60	Treatment with irbesartan reduced the risk of developing end-stage renal disease and worsening renal function in patients with type 2 DM and diabetic nephropathy
IRMA	<i>NEJM</i> 2001; 345:870-8	Irbesartan is renoprotective independently of its blood-pressure lowering effect in patients with type 2 diabetes and microalbuminuria
MDRD	<i>Ann Intern Med</i> 1995; 123:754-62	Blood pressure target for patients with proteinuria of more than 1 g/d should have a target BP of less than 125/75. For patients with proteinuria of 0.25 to 1.0 g/d should have a target BP of less than 130/80
ONTARGET	<i>Lancet</i> 2008; 372:547-53	Telmisartan and ramipril monotherapy reduced proteinuria and rise in creatinine in patients with high vascular risk; combination of the two agents led to increased acute renal failure episodes, syncope and hypotension

Trial	Reference	Results
REIN	<i>Lancet</i> 1999; 354:359-64	In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria
REIN2	<i>Lancet</i> 2005; 365:939-46	In non-diabetic nephropathy already on ACEI, no further benefit from intensified BP control (sBP/dBP < 130/80) by adding a CCB versus conventional BP control (dBP < 90) on ACEI alone
RENAAL	<i>NEJM</i> 2001; 345:861-9	Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy and was generally well-tolerated
RENAL	<i>NEJM</i> 2009; 361:1627-38	High intensity continuous renal-replacement therapy in acute kidney injury does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia
ROAD	<i>JASN</i> 2007; 18:1889-98	Up-titration of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without diabetes who had proteinuria and renal insufficiency
SHARP	<i>Lancet</i> 2011; 377:2181-92	Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo. Reduction of LDL cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily reduced the incidence of major atherosclerotic events in patients with CKD
TREAT	<i>NEJM</i> 2009; 361:2019-32	Patients with type 2 DM, CKD and anemia were randomized to darbepoetin targeting a hemoglobin of 13 g/dL or placebo. Darbepoetin did not reduce the risk of either death, a cardiovascular event or a renal event and was associated with an increased risk of stroke

## References

- Adler SG, Salant DJ. An outline of essential topics in glomerular pathophysiology, diagnosis and treatment for nephrology trainees. *Am J Kidney Dis* 2003;42:395-418.
- Andreoli TE, et al. Cecil essentials of medicine, 6th ed. Philadelphia: Saunders Publishing, 2004.
- Androgué HJ, Madias NM. Management of life threatening acid-base disorders part I. *NEJM* 1999;338:26-33.
- Androgué HJ, Madias NM. Management of life threatening acid-base disorders part II. *NEJM* 1999;338:107-111.
- Androgué HJ, Madias NE. Hyponatremia. *NEJM* 2000;342:1493-1499,1581-1589.
- Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *NEJM* 2004;351:1952-1961.
- Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, et al. Effects of losartan on renal cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *NEJM* 2001;345:861-869.
- Churchill DN, Blacke PG, Jindal KK, Toffelmire EB, Goldstein MB. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. *J Am Soc Nephrol* 1999;10(Suppl 13):S238-291.
- Donadio JV and Grande JP. Medical progress: IgA nephropathy. *NEJM* 2002;347:738-748.
- Gabow PA. Autosomal dominant polycystic kidney disease. *NEJM* 1993;329:332-342.
- Greenberg AR. Primer on kidney diseases, 3rd ed. San Diego: Academic Press, 2001.
- Hakim R, Lazarus M. Initiation of dialysis. *J Am Soc Nephrol* 1995;6:1319-1328.
- Halperin ML, Goldstein MB, Kersey R, et al. Fluid, electrolyte, and acid-base physiology: a problem-based approach, 3rd ed. New York: Harcourt Brace, 1998.
- Halperin M, Kamel K. Potassium. *Lancet* 1998;352:135-140.
- Harris SB, Meltzer SJ, Zinman B. New guidelines for the management of diabetes: a physician's guide. Steering Committee for the Revision of the Hemphill RR, et al. 1998. Review of acute renal failure. Available from: <http://www.embbbs.com/cr/rt/rt.html>.
- Hudson BG, Tryggvason K, Sundaramoorthy M, Neilson EG. Mechanisms of disease: Alport's syndrome, goodpasture's syndrome, and type IV collagen. *NEJM* 2003;348:2543-2556.
- Johnson CA, Levey AS, Coresh J, Levin A, Lau J, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults: Part II. Glomerular filtration rate, proteinuria, and other markers. *Am Fam Phys* 2004;70:1091-1097.
- Johnson RJ, Feehally J, (editors). Comprehensive clinical nephrology. New York: Mosby, 1999.
- K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification: 2000 executive update. Available from: <http://www.kidney.org/professionals/dogi/kdofi/toc.htm>
- Keane WF, Garabed E. Proteinuria, albuminuria, risk assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. *Amer J Kid Dis* 1999;33:1004-1010.
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effects of angiotensin-converting enzyme inhibition on diabetic nephropathy. *NEJM* 1993;329:1456-1462.
- McFarlane P, Tobe S, Houlden R, Harris S. Nephropathy: Canadian Diabetes Association clinical practice guidelines expert committee. 2003. Available from: <http://www.diabetes.ca/cpg2003/downloads/nephropathy.pdf>.S66-S71.
- Meltzer S, et al. Clinical practice guidelines for the management of diabetes in Canada. *CMAJ* 1998;159:973-978.
- Myers A. Medicine, 4th ed. Baltimore: Lippincott Williams & Wilkins, 2001.
- ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *NEJM* 2008;358:1547-1559.
- Sabatine M. Pocket medicine: The Massachusetts General Hospital handbook of internal medicine, 2nd ed. New York: Lippincott Williams & Wilkins, 2004. Chapter 4; p1-20.
- Schiffl H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *NEJM* 2002;346:305-310.
- Schreiber M. Seminars for year 3 University of Toronto Medicine clinical clerks on medicine: hyponatremia and hypernatremia. October 29, 2002.
- Smith K. Renal disease: a conceptual approach. New York: Churchill Livingstone, 1987.
- Thadhani R, Pascual M, Bonventre JV. Acute renal failure. *NEJM* 1996;334:1448-1460.

Matthew Gladman and Russell Rasquinha, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Esther Bui, Dr. Brian Murray and Dr. David Tang-Wai, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Movement Disorders</b> . . . . .	<b>24</b>
<b>The Neurological Exam</b> . . . . .	<b>2</b>	Overview of Movement Disorders	
General Exam and Mental Status		Function of the Basal Ganglia	
Cranial Nerves Exam		Movement Disorders	
Motor Exam		Parkinson's Disease (PD)	
Sensory Exam		Other Parkinsonian Disorders	
Coordination Exam and Gait		Huntington's Disease	
<b>Basic Anatomy Review</b> . . . . .	<b>4</b>	Dystonia	
<b>Lumbar Puncture</b> . . . . .	<b>7</b>	Tic Disorders	
<b>Approach to Common Presentations</b> . . . . .	<b>7</b>	Tourette's Syndrome	
Weakness		<b>Cerebellar Disorders</b> . . . . .	<b>28</b>
Numbness/Altered Sensation		Wernicke-Korsakoff Syndrome	
<b>Cranial Nerve Deficits</b> . . . . .	<b>8</b>	Cerebellar Ataxias	
CN I: Olfactory		<b>Vertigo</b> . . . . .	<b>OT12</b>
CN II: Optic		<b>Gait Disturbances</b> . . . . .	<b>29</b>
CN III: Oculomotor		<b>Motor Neuron Disease</b> . . . . .	<b>30</b>
CN IV: Trochlear		Amyotrophic Lateral Sclerosis (ALS)	
CN V: Trigeminal		Other Motor Neuron Diseases	
CN VI: Abducens		<b>Peripheral Neuropathies</b> . . . . .	<b>31</b>
CN VII: Facial		<b>Neuromuscular Junction Diseases</b> . . . . .	<b>32</b>
CN VIII: Vestibulocochlear		Clinical Approach	
CN IX: Glossopharyngeal		Myasthenia Gravis (MG)	
CN X: Vagus		Lambert-Eaton Myasthenic Syndrome (LEMS)	
CN XI: Accessory		Botulism	
CN XII: Hypoglossal		<b>Myopathies</b> . . . . .	<b>34</b>
<b>NEURO-OPHTHALMOLOGY</b> . . . . .	<b>11</b>	Clinical Approach	
<b>Abnormalities of Vision</b> . . . . .	<b>11</b>	Polymyositis/Dermatomyositis	
Acute Visual Loss		Myotonic Dystrophy	
Optic Neuritis		Duchenne and Becker Muscular Dystrophy	
Anterior Ischemic Optic Neuropathy		<b>Pain Syndromes</b> . . . . .	<b>35</b>
Amaurosis Fugax		Approach to Pain Syndromes	
Central Retinal Vein Occlusion (CRVO)		Neuropathic Pain	
Optic Disc Edema		Tic Douloureux (Trigeminal Neuralgia)	
Optic Disc Atrophy		Postherpetic Neuralgia (PHN)	
<b>Abnormalities of Visual Field</b> . . . . .	<b>12</b>	Painful Diabetic Neuropathy	
<b>Abnormalities of Eye Movements</b> . . . . .	<b>13</b>	Complex Regional Pain Syndromes (CRPS)	
Disorders of Gaze		<b>Headache</b> . . . . .	<b>38</b>
Internuclear Ophthalmoplegia (INO)		Migraine Headaches	
Diplopia		<b>Sleep Disorders</b> . . . . .	<b>41</b>
Nystagmus		Overview of Sleep	
<b>Abnormalities of Pupils</b> . . . . .	<b>14</b>	Disturbances of Alertness and Sleep	
<b>Seizure Disorders and Epilepsy</b> . . . . .	<b>14</b>	<b>CNS Infections</b> . . . . .	<b>ID19</b>
Seizure		<b>Spinal Cord Syndromes</b> . . . . .	<b>NS26</b>
Status Epilepticus		<b>Stroke</b> . . . . .	<b>43</b>
<b>Behavioural Neurology</b> . . . . .	<b>17</b>	Terminology	
Acute Confusional State/Delirium		Pathophysiology	
Dementia		Assessment and Treatment of Ischemic Stroke	
Alzheimer's Disease (AD)		Primary and Secondary Prevention of Ischemic Stroke	
Dementia with Lewy Bodies (DLB)		Cerebral Hemorrhage	
Frontotemporal Dementia (FTD)		<b>Multiple Sclerosis (MS)</b> . . . . .	<b>46</b>
Creutzfeldt-Jakob Disease (CJD)		<b>Common Medications</b> . . . . .	<b>48</b>
Normal Pressure Hydrocephalus (NPH)		<b>Landmark Neurology Trials</b> . . . . .	<b>50</b>
Aphasia		<b>References</b> . . . . .	<b>50</b>
Apraxia			
Agnosia			
<b>Mild Traumatic Brain Injury</b> . . . . .	<b>22</b>		
<b>Neuro-oncology</b> . . . . .	<b>23</b>		
Paraneoplastic Syndrome			
Tumours of the Nervous System			

## Acronyms

ACA	anterior cerebral artery	DLB	dementia with Lewy bodies	LGB	lateral geniculate body	PCOMM	Posterior Communicating Artery
AD	Alzheimer's disease	EOM	extraocular movement	LMN	lower motor neuron	PICA	posterior inferior cerebral artery
ADL	activities of daily living	FEF	frontal eye field	LOC	level of consciousness	PPRF	paramedian pontine reticular formation
AION	acute ischemic optic neuropathy	FTD	frontotemporal dementia	MCA	middle cerebral artery	RAPD	relative afferent pupillary defect
ALS	amyotrophic lateral sclerosis	GBS	Guillain-Barré syndrome	MG	myasthenia gravis	REM	rapid eye movement
AVM	arteriovenous malformation	GCA	giant cell arteritis	MLF	medial longitudinal fasciculus	ROM	range of motion
AVPU	alert, verbal, pain, unresponsive	GCS	Glasgow coma scale	MMSE	mini mental status examination	SAH	subarachnoid hemorrhage
CJD	Creutzfeldt-Jakob disease	IADL	instrumental activities of daily living	MoCA	Montreal cognitive assessment	TBI	traumatic brain injury
CN	cranial nerve	ICH	intracranial hemorrhage	MS	multiple sclerosis	TIA	transient ischemic attack
CRVO	central retinal vein occlusion	IIH	idiopathic intracranial hypertension	NCS	nerve conduction studies	UMN	upper motor neuron
CSF	cerebral spinal fluid	IVIg	intravenous immunoglobulin	NPH	normal pressure hydrocephalus	VEGF	vascular endothelial growth factor
DBS	deep brain stimulation	LEMS	Lambert-Eaton myasthenic syndrome	PD	Parkinson's disease		

## The Neurological Exam

### General Exam and Mental Status



- **vitals:** pulse (especially rhythm), BP, temperature
- **H&N:** meningismus, head injury/bruises, (signs of basal skull fracture: Battle's sign, raccoon eyes, hemotympanum, rhinorrhea), tongue biting
- **CVS:** carotid bruits, heart murmurs
- **mental status:** orientation (person, place, time), LOC (GCS)
  - GCS/15 – Motor/6, Verbal/5 (T= intubated), Eyes/4
- **cognition:**
  - Folstein MMSE – /30 ( $\leq 24$  indicative of dementia)
  - MoCA – /30 ( $\geq 26$  is considered normal)
  - frontal lobe testing (for perseveration)
  - clock drawing



Visit Online Atlas for Cranial Nerve Exam, Motor Exam, Sensory Exam Examination Techniques.



Battle's sign = mastoid ecchymosis

Raccoon eyes = periorbital ecchymosis



When testing CN1, avoid noxious smells like ammonia, as this tests CNV.



If patient has not brought their glasses, have them look through a pinhole for best corrected vision.



**CN Innervation of EOM**  
LR: CNVI, SO: CNIV, Other: CN3.



Contraction of the left sternocleidomastoid turns the head right.



**Caloric Reflexes**  
Describe nystagmus by direction of fast component

#### COWS

Cold  
Opposite  
Warm  
Same



#### Upper Motor Neuron Tests

**Babinski Reflex:** 'Up-going' big toe  $\pm$  fanning of toes indicates an UMN lesion.

**Hoffman Reflex:** Flexion of IP joint of the thumb when tapping the nail of the index or ring finger may indicate an UMN lesion if asymmetrical.

**Pronator Drift:** Patients are unable to maintain arm extension and supination in an UMN lesion.

### Cranial Nerves Exam

- **olfactory (CNI):** odour sensation (test each nostril separately)
- **optic (CNII)**
  - a. visual acuity: test each eye individually using best corrected vision
  - b. visual fields
  - c. pupil: direct and consensual pupillary reaction (afferent limb), accommodation, swinging flashlight test (see *Relative Afferent Pupillary Defect*, [Ophthalmology](#), OP33)
  - d. funduscopy: optic disc edema, optic disc pallor, venous pulsations, hemorrhages
- **extra ocular movements (EOM)**
  - a. **oculomotor (CNIII):** levator palpebrae superioris, medial rectus, superior rectus, inferior rectus, inferior oblique, efferent limb of pupillary light response
  - b. **trochlear (CNIV):** superior oblique
  - c. **abducens (CNVI):** lateral rectus
- **trigeminal (CNV)**
  - a. sensory: V1 (above supraorbital ridge), V2 (buccal area), V3 (mandible), corneal reflex (afferent)
  - b. motor: temporalis, masseter, pterygoids, jaw jerk reflex
- **facial (CNVII)**
  - a. sensorimotor: muscles of facial expression, hyperacusis (stapedius), corneal reflex (efferent)
  - b. visceral sensory: taste of anterior 2/3 of tongue
  - c. visceral motor: salivary and lacrimal glands
- **vestibulocochlear (CNVIII)**
  - a. vestibular: nystagmus, caloric reflexes
  - b. cochlear: Rinne, Weber
- **glossopharyngeal (CNIX) and vagus (CNX):** palatal elevation, gag reflex, vocal cord function, swallowing, taste of posterior third of tongue
- **accessory (CNXI):** trapezius and sternocleidomastoid strength
- **hypoglossal (CNXII):** tongue muscle bulk, fasciculations, strength

### Motor Exam

- **bulk:** atrophy, asymmetry
- **abnormal movements:** tremors, chorea, dystonia, dyskinesia, hemiballism, myoclonus, athetosis, tics, fasciculations
- **abnormal posturing:** decerebrate, decorticate
- **tone:** hypotonia (flaccid), hypertonia (spasticity, rigidity, paratonia), cogwheeling
- **strength**
- **reflexes:** deep tendon reflexes, abdominal reflexes, primitive reflexes, Babinski, Hoffman, clonus

Table 1. Localization of Motor Deficits

	LMN	UMN	Extrapyramidal
<b>Muscle Tone</b>	Flaccid	Spastic	Rigid
<b>Involuntary Movements</b>	Fasciculations	None	Present (e.g. tremor)
<b>Reflexes</b>	Decreased	Increased	Normal
<b>Plantar Reflex</b>	Down-going (flexor)	Up-going (extensor)	Down-going (flexor)
<b>Pattern of Muscle Weakness</b>	Proximal, distal or focal	<b>Upper extremities:</b> extensors weaker than flexors <b>Lower extremities:</b> flexors weaker than extensors	None

Table 2. Overview of Neuromuscular Diseases

	Upper and Lower Motor Neuron Disease	Peripheral Neuropathy	Neuromuscular Junction	Myopathy
<b>SIGNS AND SYMPTOMS</b>				
Weakness	Segmental and asymmetrical, distal → proximal	Distal (except GBS) but may be asymmetrical	Proximal and fatiguable	Proximal
Fasciculations	Yes	Yes	No	No
Reflexes	Increased	Decreased/absent	Normal	Normal (until late)
Sensory	No	Yes	No	No
Autonomic*	No	Yes	No	No
<b>TESTS</b>				
EMG	Denervation and reinnervation	Signs of demyelination ± axonal loss	Decremental response in MG Jitter on single fibre EMG	Small, short motor potentials
NCS	Normal	Abnormal	Normal	Normal
Muscle enzyme	Normal	Normal	Normal	Increased

\*e.g. orthostatic hypotension, anhydrosis, visual blurring, urinary hesitancy or incontinence, constipation, erectile dysfunction

Table 3. Approach to Strength Testing of Radiculopathies versus Peripheral Neuropathies

How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, all associated peripheral nerves (and their movements) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerve. Especially useful peripheral nerve "pairs" are bolded for emphasis.

Root	Peripheral Nerve	Movement	Muscle
C5	Axillary	Shoulder abduction	Deltoid
C6	Musculocutaneous (C5/6) Radial (C6)	Elbow flexion Elbow flexion Wrist extension	Biceps Brachioradialis Extensor carpi radialis longus
C7	Radial Posterior interosseus	Elbow extension Finger extension	Triceps Extensor digitorum communis
C8, T1	<b>Median</b>  <b>Ulnar</b>	Thumb flexion Thumb abduction Opposition Finger abduction	Flexor pollicis longus (look for thenar wasting) Abductor pollicis brevis (look for thenar wasting) Opponens pollicis (look for thenar wasting) First dorsal interosseus (look for wasting in first dorsal webbed space)
L2, 3, 4	<b>Femoral</b> <b>Obturator</b>	Hip flexion Hip adduction	Iliopsoas Adductor muscles
L3, 4	Femoral (L3/4) Deep peroneal (L4/5)	Knee extension Dorsiflexion	Quadriceps Tibialis anterior
L5	Sciatic (L5, S1) <b>Tibial</b> <b>Superficial peroneal</b> Deep peroneal	Hip extension Ankle inversion Ankle eversion Big toe extension	Gluteus maximus Tibialis posterior Peroneal muscles
S1	Sciatic Tibial	Knee flexion Plantar flexion	Hamstring muscles Gastrocnemius and soleus



#### Pyramidal Pattern of Muscle Weakness (i.e. UMN)

Weaker arm extensors: shoulder abduction, elbow extension, wrist extension, finger extension, finger abduction.

Weaker leg flexors: hip flexion, knee flexion, ankle dorsiflexion.



#### MRC Muscle Strength Scale

- 5 Full power
- 4 Submaximal power against resistance (ranging 4+, 4, 4-)
- 3 Full ROM against gravity without resistance
- 2 Full ROM with gravity removed
- 1 Muscle flicker
- 0 No muscle contraction



#### Primitive Reflexes

Grasp, palmomental, root, glabellar tap, snout.



#### Deep Tendon Reflexes

Root	Muscle Tendon
------	---------------

C5/6	Biceps
C6	Brachioradialis
C7	Triceps
C8	Finger flexors
L2/3	Hip adductors
L3/4	Knee extensors
S1/2	Plantar flexion



#### Deep Tendon Reflex Scoring

0	Absent
1+	Depressed
2+	Normal
3+	Increased
4+	Clonus (≥4 beats)

## Sensory Exam

- **primary sensation**
  - spinothalamic tract: pain and temperature
  - dorsal column: proprioception and vibration
- **cortical sensation**
  - graphesthesia, stereognosis, extinction, 2-point discrimination



## Coordination Exam and Gait

- **coordination exam**
  - finger-to-nose, heel-to-shin, rapid alternating movements, “scanning” speech
- **stance and gait**
  - gait: antalgic, hemiplegic, ataxic, apraxic, festination, foot drop, broad-based
  - tandem gait (heel-to-toe walking)
  - Romberg test
  - pull test for retropulsion



A slow or uncoordinated rapid alternating movement can also be a sign of subtle weakness or Parkinsonism.



### Romberg Test

Stable with eyes open and closed = normal.

Stable with eyes open, falls with eyes closed = +ve Romberg, suggesting loss of joint position sense.

## Basic Anatomy Review

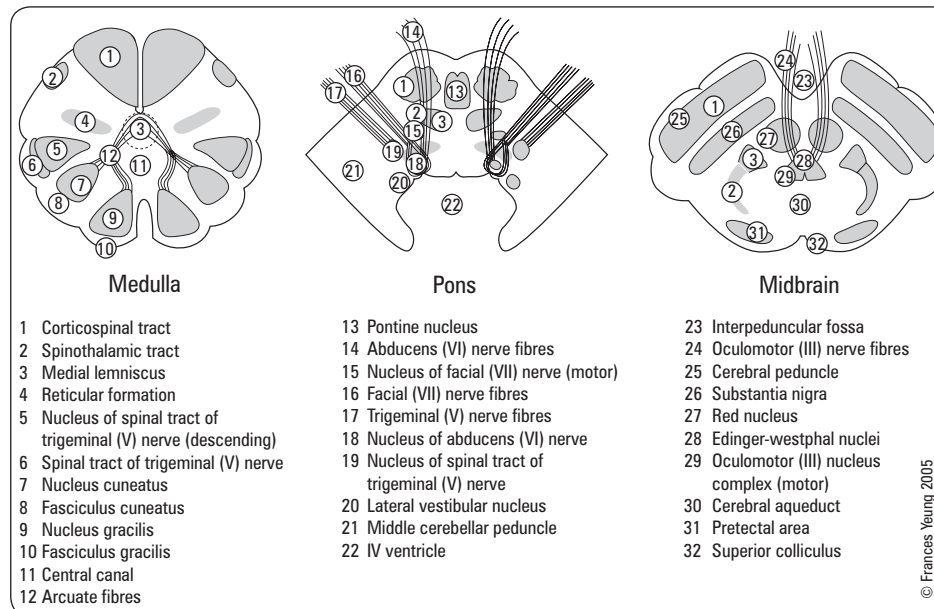


Figure 1. Brainstem (axial view)

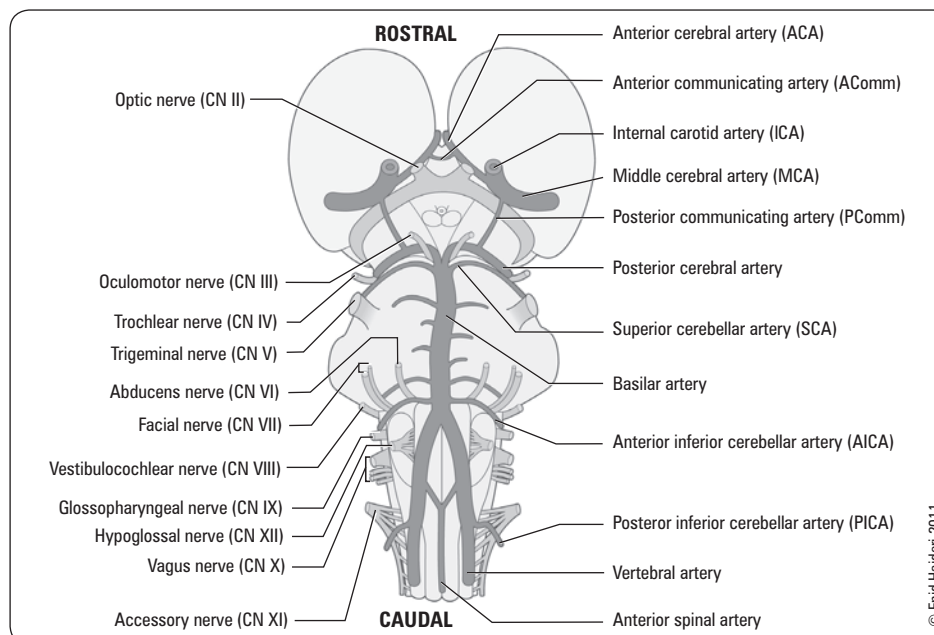


Figure 2. Brainstem (posterior view)



See Functional Neuroanatomy software

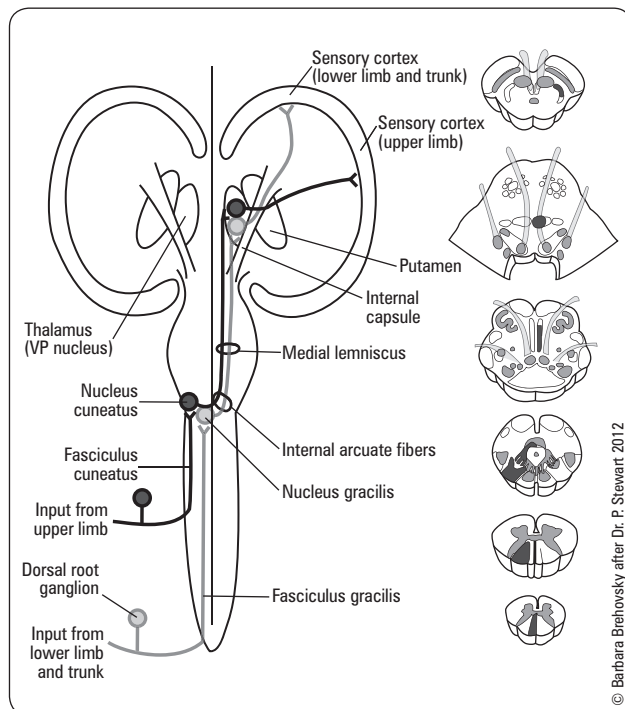


Figure 3. Discriminative touch pathway (dorsal column) from body

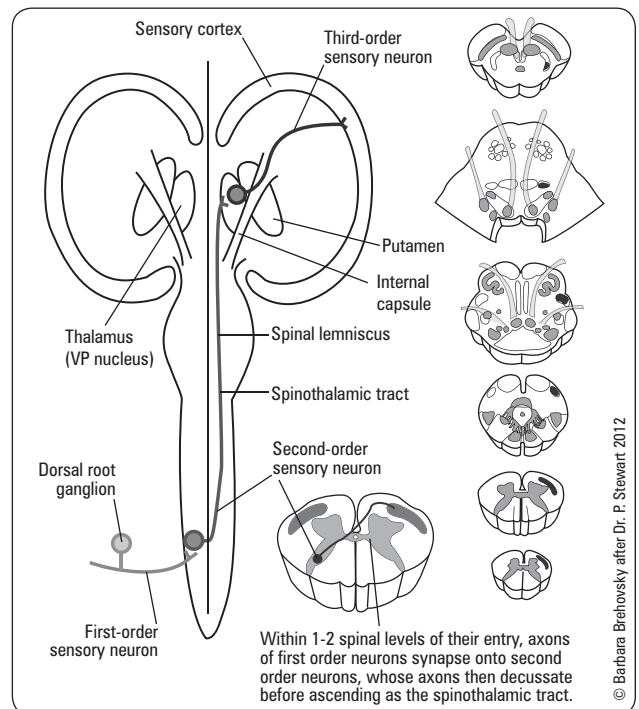


Figure 4. Spinothalamic tract from body

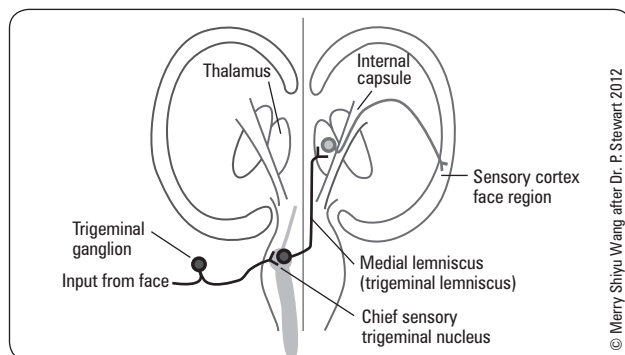


Figure 5. Discriminative touch pathway (dorsal column) from face

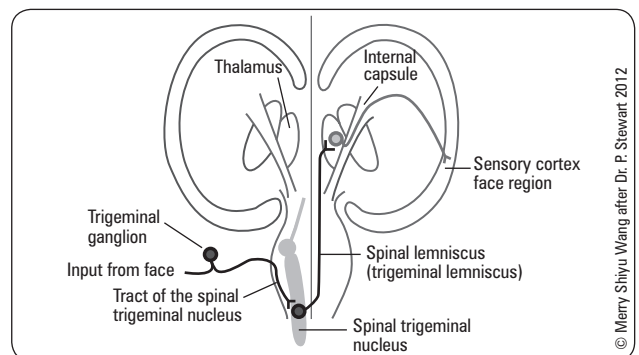


Figure 6. Spinothalamic tract pathway from face

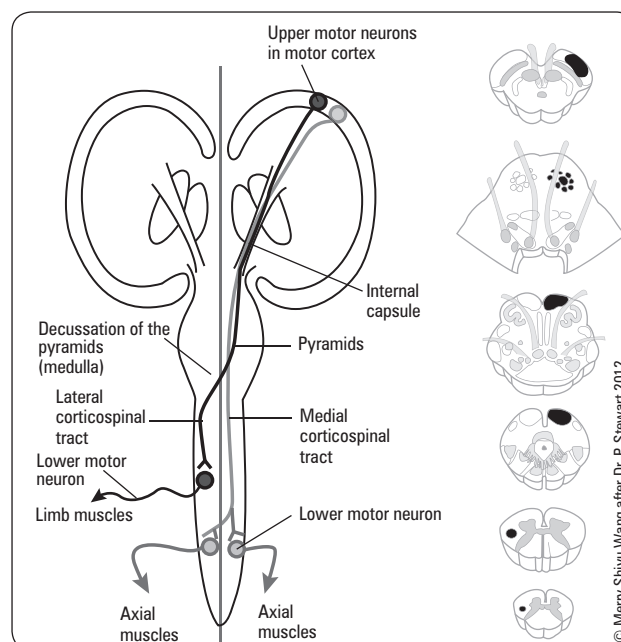


Figure 7. Corticospinal motor pathway

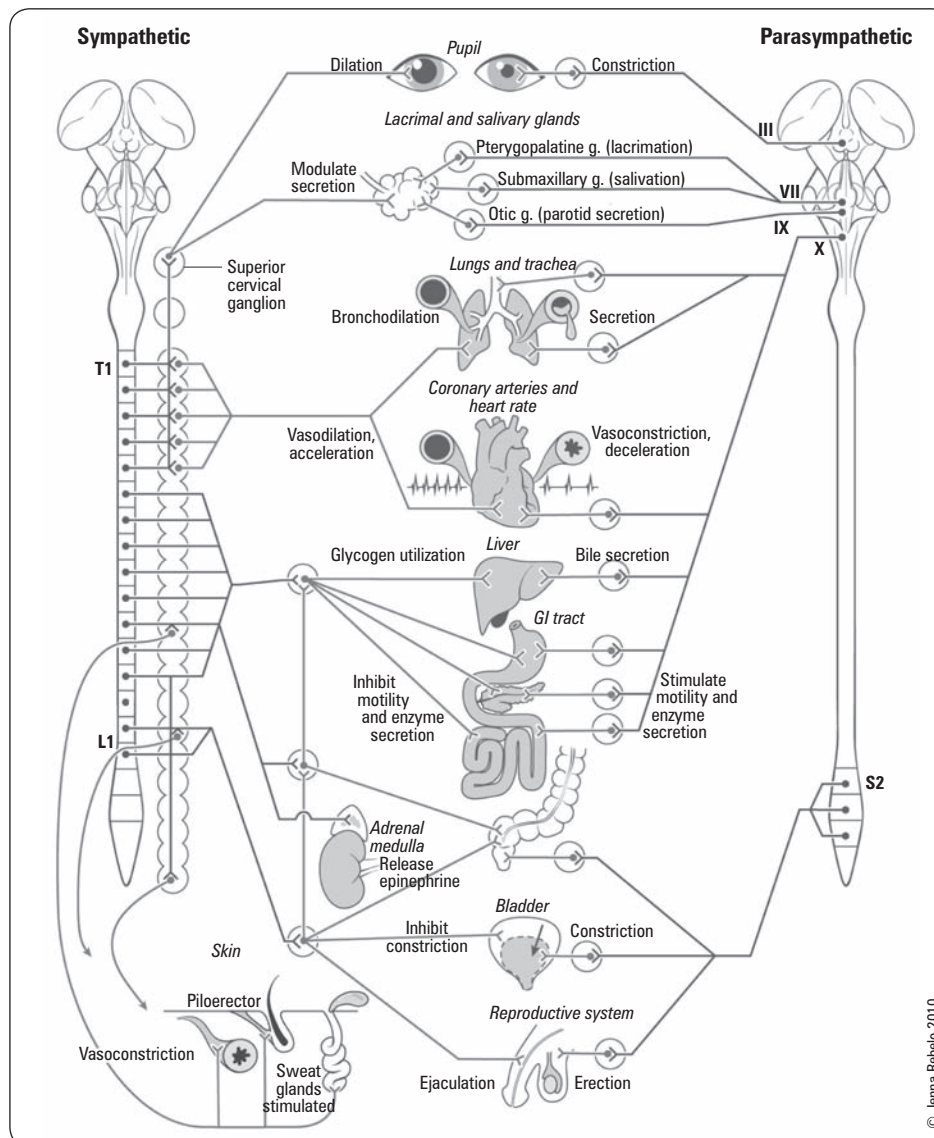


Figure 8. Sympathetic and parasympathetic pathway

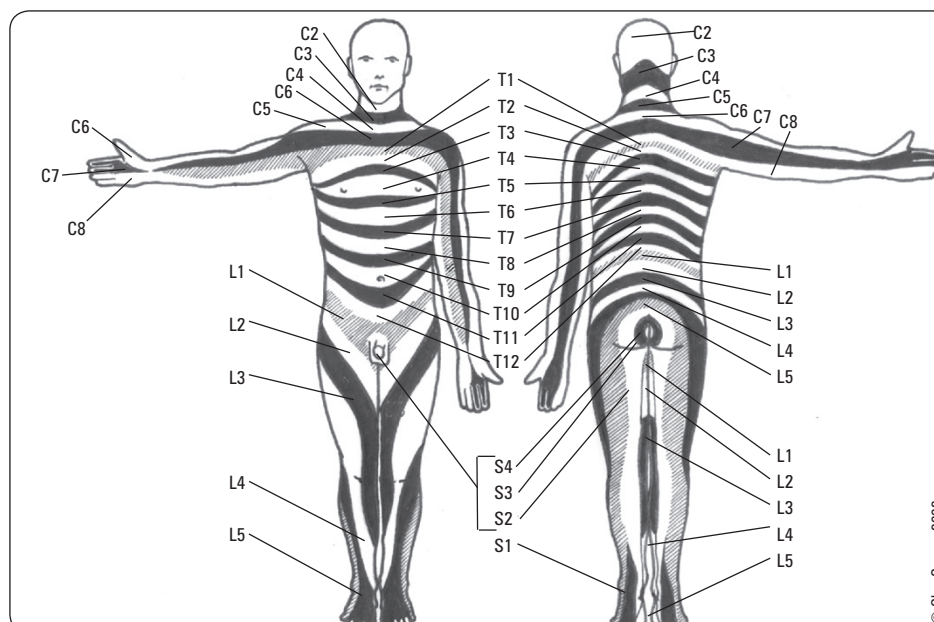


Figure 9. Dermatome map

**Myotomes**

- C5 – Shoulder abduction/elbow flexion
- C6 – Wrist extensors
- C7 – Elbow extension
- C8 – Squeeze hand
- T1 – Abduct fingers
- T2-9 – Intercostal (abdominal reflexes)
- T9-10 – Upper abdominals
- T11-12 – Lower abdominals
- L2 – Flex hip
- L3 – Hip adduction
- L4 – Knee extension and ankle dorsiflexion
- L5 – Ankle dorsiflexion and big toe extension
- S1 – Plantarflexion

# Lumbar Puncture

## Indications

- diagnostic: CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barré, vasculitis), subarachnoid hemorrhage (if CT negative), CNS neoplasm (neoplastic meningitis)
- therapeutic: to administer anesthesia, chemotherapy, contrast media; to decrease intracranial pressure (pseudotumour cerebri, normal pressure hydrocephalus)

## Contraindications

- mass lesion causing increased intracranial pressure (ICP) – could lead to cerebral herniation
  - require CT first
- infection over lumbar puncture (LP) site/suspected epidural abscess
- low platelets (<50,000) or treatment with anticoagulation (high INR or aPTT)
- uncooperative patient

## Complications

- tonsillar herniation
- post-LP headache (5-40%): worse when upright, better supine; generally onset within 24 h
  - prevention: smaller gauge (i.e. 22) needle, reinsert stylet prior to needle removal, blunt-ended needle
  - symptomatic treatment: caffeine and sodium benzoate injection
  - corrective treatment: blood patch (autologous)
- spinal epidural hematoma
- infection

## What to send LP for

- **tube #1: cell count and differential:** RBCs, WBCs and differential
  - xanthochromia (yellow bilirubin pigmentation implies recent bleed into CSF)
- **tube #2: chemistry:** glucose (compare to serum glucose) and protein
- **tube #3: microbiology:** Gram stain and C&S
  - specific tests depending on clinical situation/suspicion
    - ♦ viral: PCR for herpes simplex virus (HSV) and other viruses
    - ♦ bacterial: polysaccharide antigens of *H. influenzae*, *N. meningitidis*, *S. pneumoniae*
    - ♦ fungal: Cryptococcal antigen, India ink stain (cryptococcus), culture
    - ♦ TB: acid-fast stain, TB culture, TB PCR
- **tube #4: cytology:** for evidence of malignant cells
- **tube #5: cell count:** compare RBC count to that of tube #1
  - **note:** tube 4 or 5 can be sent for repeat cell count

Table 4. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes)

Condition	Colour	Protein	Glucose	Cells
<b>NORMAL</b>	Clear	<0.45 g/L	60% of serum glc or >3.0 mmol/L	0-5 WBC, 0 RBC, 0 PMNs
<b>INFECTIOUS</b>				
<b>Viral infection</b>	Clear or opalescent	Normal or slightly increased <0.45-1 g/L	Normal	<1000x10 <sup>6</sup> /L Lymphocytes mostly, some PMNs
<b>Bacterial infection</b>	Opalescent yellow, may clot	>1 g/L	Decreased (<25% serum glc or <2.0 mmol/L)	>1000x10 <sup>6</sup> /L PMNs
<b>Granulomatous infection</b> (tuberculosis, fungal)	Clear or opalescent	Increased but usually <5 g/L	Decreased (usually <2.0-4.0 mmol/L)	<1000x10 <sup>6</sup> /L Lymphocytes



The needle for a lumbar puncture is inserted into one of L3-4, L4-5 or L5-S1 interspaces.



Do not delay antibiotics while waiting for a lumbar puncture if infection is suspected.



RBCs in tube #1 > #5 → traumatic tap  
RBCs in tube #1 = #5 → SAH

# Approach to Common Presentations



## Weakness

### Approach

- **mode of onset:** abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (hereditary, degenerative, endocrinologic, neoplastic)
- **course:** worse at onset (vascular), progressive (neoplastic, degenerative, infective), episodic (vascular, inflammatory), activity dependent (NMJ, muscular)
- **pattern:** objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
- **associated symptoms:** sensory symptoms, cortical symptoms, spinal symptoms (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
- **history:** family history, developmental history, medications, risk factors, recent/preceding exposures
- **investigations for LMN:** NCS/EMG
- **investigations for UMN:** imaging (brain and/or spinal cord)

### Differential Diagnosis

- objective muscle weakness
  - generalized:
    - ♦ myopathy (muscular dystrophy, polymyositis, vasculitis, collagen vascular, HIV, CMV, influenza, steroids, statins, alcohol, hypothyroidism, Cushing's syndrome, electrolyte disorders)
    - ♦ NMJ (MG, botulism, LEMS, organophosphate poisoning)
    - ♦ cachexia
  - localized:
    - ♦ UMN (leukodystrophy, vasculitis, abscess, brain tumour, vitamin B<sub>12</sub> deficiency, MS, stroke)
    - ♦ anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic, lead toxicity)
    - ♦ peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
- no objective muscle weakness
  - chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  - depression, deconditioning
- if loss of passive motion, consider intra-articular, peri-articular or extra-articular causes

## Numbness/Altered Sensation

### Approach

- positive sensory symptoms: paresthesia/dysesthesia= tingling, pins and needles, prickling, burning, stabbing
- negative sensory symptoms: hypoesthesia/anaesthesia= numbness, diminution or absence of feeling
- determine distribution of sensory loss: nerve root vs. peripheral nerve
- investigations: NCS, vitamin B<sub>12</sub> levels, imaging based on associated findings

### Differential Diagnosis

- cerebral: stroke, demyelination, tumour
  - associated symptoms: hemiplegia, aphasia, apraxia
- brainstem: stroke, demyelination, tumour
  - associated symptoms: diplopia, vertigo, dysarthria, dysphagia
- spinal cord/radiculopathy: cord infarction, tumour, MS, syringomyelia, vitamin B<sub>12</sub> deficiency, disc lesion
  - associated symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern)
- neuropathy: focal compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, B<sub>12</sub> deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid

## Cranial Nerve Deficits



### CN I: Olfactory Nerve

#### Clinical Features

- absence of sense of smell associated with a loss of taste

#### Differential Diagnosis

- **nasal:** physical obstruction
  - heavy smoking, chronic rhinitis, sinusitis, neoplasms, septal deformity, choanal atresia, vestibular stenosis, foreign body
- **olfactory neuroepithelial:** destruction of receptors or their axon filaments
  - influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
- **central:** lesion of olfactory pathway
  - Kallmann's syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeal inflammation, meningioma, aneurysm, PD, stroke, MS
- **endocrine/metabolic**
  - DM, adrenal hypo/hyperfunction, pseudohypoparathyroidism, hypothyroidism, renal/liver failure, vitamin deficiency



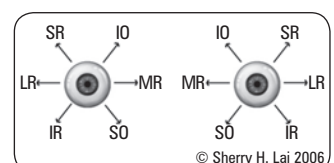
If anosmia is not associated with loss of taste, consider malingering.



Kallmann's syndrome is a congenital disorder of anosmia and hypogonadotropic hypogonadism.

### CN II: Optic Nerve

- see *Neuro-Ophthalmology*, N11



**Figure 10. Diagnostic positions of gaze to isolate primary action of each muscle**



## CN III: Oculomotor Nerve

### Clinical Features

- ptosis, resting eye position is “down and out” (depressed and abducted), pupil dilated (mydriasis)
- vertical and horizontal diplopia; paralysis of adduction, elevation and depression

### Differential Diagnosis

- PCOMM aneurysm:** early mydriasis, then CN III palsy
- cavernous sinus** (internal carotid aneurysm, meningioma, sinus thrombosis): associated with deficits in other CNs near the cavernous sinus (see Figure 11)
- ischemia of CNIII** (DM, temporal arteritis, HTN, atherosclerosis): pupil sparing CN III palsy
- midbrain lesion:** complete unilateral CNIII palsy with bilateral weakness of the superior rectus and ptosis with contralateral pyramidal signs  $\pm$  mydriasis
- orbital lesion:** associated with optic neuropathy, chemosis, proptosis
- other** (inflammatory, infection, neoplasia, uncal herniation, trauma)

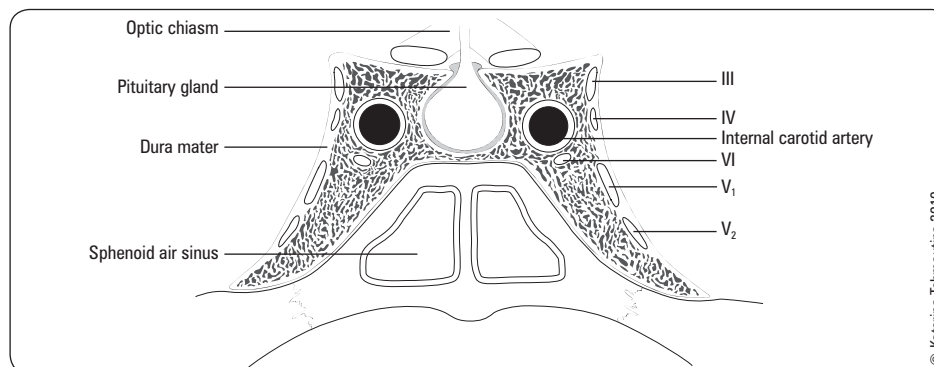


Figure 11. Cavernous sinus (coronal view)



Pupillary constrictor fibres run along outside of nerve, whereas vasculature is contained within nerve.  
For CN III palsy with a reactive pupil, always think ischemic cause (“pupil sparing”).  
For CN III palsy with mydriasis, think compressive lesion.



### DDx of CNIII Palsy

**iCAM**  
ischemic  
Cavernous sinus  
Aneurysm (PCOMM, IC)  
Midbrain lesion



Lesions involving the cavernous sinus can lead to cranial nerve palsies of III, IV, VI, V1 and V2 as well as orbital pain and proptosis.



CN IV is the only cranial nerve that crosses the midline and exits posteriorly. A CN IV lesion may cause a contralateral deficit.



CN IV is at risk of trauma during neurosurgical procedures involving the midbrain because of its long intracranial course.



Jaw deviation is towards the side of a LMN CN V lesion.



### Distinguishing CN III, IV, and VI Lesions

	III	IV	VI
<b>Diplopia</b>	Oblique	Vertical	Horizontal
<b>Exacerbating</b>	Near target	Looking down	Far target
<b>Head tilt</b>	Up and rotated away	Down and flexed away	Rotated towards



CN VI has the longest intracranial course and is vulnerable to increased ICP, creating a false localizing sign.

## CN IV: Trochlear Nerve

### Clinical Features

- vertical and torsional diplopia; defect of intorsion and depression
- patient may complain of difficulty going down stairs or reading

### Differential Diagnosis

- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, superior orbital fissure (tumour, granuloma)

## CN V: Trigeminal Nerve

### Clinical Features

- ipsilateral facial numbness, weakness of muscles of mastication (V3 only) with pterygoid deviation towards the side of the lesion

### Differential Diagnosis

- brainstem** (ischemia, tumour, syringobulbia, demyelination)
- peripheral** (tumour, aneurysm, chronic meningitis, metastatic infiltration of nerve)
- trigeminal ganglion** (acoustic neuroma, meningioma, fracture of middle fossa)
- cavernous sinus** (carotid aneurysm, meningioma, sinus thrombosis)
- trauma**
- note: other CN V lesions that cause facial pain = trigeminal neuralgia, herpes zoster

## CN VI: Abducens Nerve

### Clinical Features

- resting inward deviation (esotropia)
- horizontal diplopia; defect of lateral gaze

### Differential Diagnosis

- pons** (infarction, hemorrhage, demyelination, tumour): associated with facial weakness and contralateral pyramidal signs
- tentorial orifice** (compression, meningioma, trauma): false localizing sign of increased ICP
- cavernous sinus** (carotid aneurysm, meningioma, sinus thrombosis)
- ischemia of CN VI** (DM, temporal arteritis, HTN, atherosclerosis)
- congenital** (Duane's syndrome)



## CN VII: Facial Nerve

### Clinical Features

- LMN lesion: ipsilateral facial weakness (facial droop, flattening of forehead, inability to close eyes, flattening of nasolabial fold)
- UMN lesion: contralateral facial weakness with forehead sparing (due to bilateral frontalis innervation)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

### Differential Diagnosis

- **idiopathic** = Bell's Palsy, 80-90% of cases (see [Otolaryngology](#), OT22)
  - most often related to HSV, but other viruses may be implicated (CMV, herpes zoster, EBV)
- **other**: temporal bone fracture, EBV, Ramsay-Hunt (HSV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease, Lyme meningitis, HIV

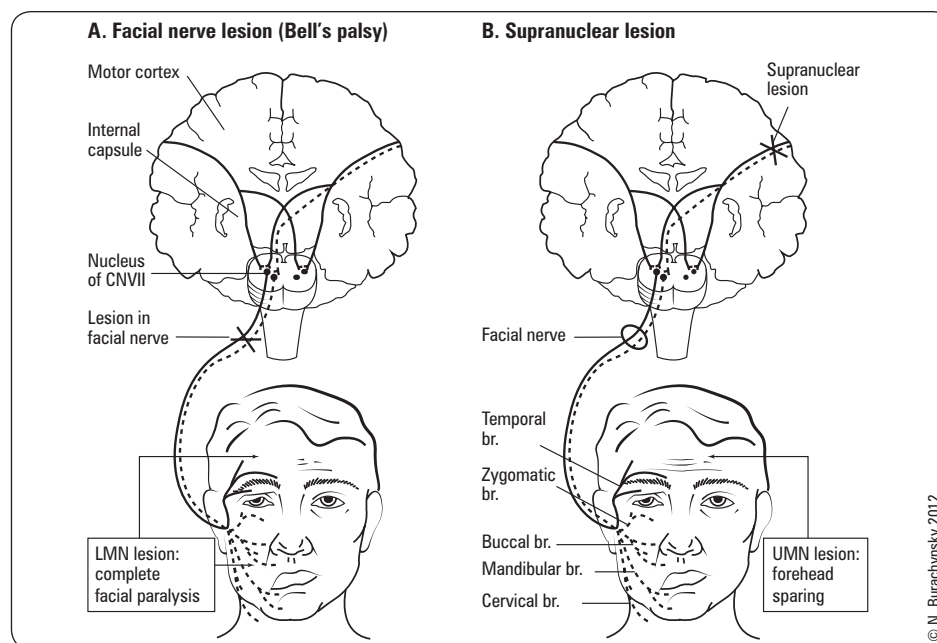


Figure 12. UMN vs. LMN facial nerve palsy

## CN VIII: Vestibulocochlear Nerve

- see [Otolaryngology](#), OT12

## CN IX: Glossopharyngeal Nerve

### Clinical Features

- unilateral lesion is rare
- taste dysfunction in posterior 1/3 of tongue
- absent gag reflex and dysphagia

### Disorders

- **glossopharyngeal neuralgia**: sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
  - treated with carbamazepine or surgical ablation of CN IX

## CN X: Vagus Nerve

### Clinical Features

- oropharyngeal dysphagia (transfer dysphagia) due to palatal and pharyngeal weakness
  - neuromuscular causes of dysphagia:
    - ♦ CNS: stroke, cerebral palsy, tumour, trauma, PD, AD, MS
    - ♦ CN: DM, laryngeal nerve palsy, polio, ALS
    - ♦ myopathic/NMJ: dermatomyositis, polymyositis, MG, sarcoidosis
  - other causes of dysphagia: see [Gastroenterology](#), G8
- dysarthria: inability to produce understandable speech due to impaired phonation and/or resonance



Forehead is spared in a UMN CN VII lesion due to bilateral innervation of CN VII nuclei from cerebral hemispheres for the frontalis.



### Facial Nerve Branch Memory Aid

#### To Zanzibar By Motor Car

Temporal  
Zygomatic  
Buccal  
Mandibular  
Cervical



When screening for dysphagia and assessing aspiration risk, the presence of a gag reflex is insufficient. The correct screening test is to observe the patient drinking water from a cup while observing for any coughing, choking, or "wetness" of voice.



### Differential Diagnosis of Lower Cranial Nerve Deficits (CN IX, X, XI, XII)

**Intracranial/skull base**: meningioma, neurofibroma, metastases, osteomyelitis, meningitis.  
**Brainstem**: stroke, demyelination, syringobulbia, poliomyelitis, astrocytoma.  
**Neck**: trauma, surgery, tumours.



Normal swallowing is initiated when the tongue moves a bolus back into the palatal archway. Tongue movements are innervated exclusively by CN XII. The bolus stimulates the soft palate to elevate and the bolus is deflected into the oropharynx. Next the pharyngeal constrictors contract, the larynx elevates, and the vocal cords close. Swallowing depends on afferent information via CN V, IX, and X and motor action via CN V, VII, IX, X, and XII.

Connections in the nucleus of the tractus solitarius in the medulla (in proximity to the respiratory centre), act as the swallowing centre. Swallowing and breathing are coordinated to prevent aspiration.



Uvula deviation is **away from** the side of a LMN CN X lesion due to impaired ipsilateral palatal elevation.

## CN XI: Accessory Nerve

### Clinical Features

- LMN lesion: paralysis of ipsilateral trapezius and sternocleidomastoid (ipsilateral shoulder drop, weakness on turning head to contralateral side)
- UMN lesion: paralysis of ipsilateral sternocleidomastoid and contralateral trapezius



CN XI is vulnerable to damage during neck surgery.

## CN XII: Hypoglossal Nerve

### Clinical Features

- LMN lesion: tongue deviation towards lesion; ipsilateral tongue atrophy and fasciculations (if chronic)
- UMN lesion: tongue deviation away from lesion; absence of atrophy and fasciculations



Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a medial medullary infarction.

## NEURO-OPHTHALMOLOGY

### Abnormalities of Vision

- see [Ophthalmology](#), OP3



### Acute Visual Loss

- see [Ophthalmology](#), OP3

### Optic Neuritis

- see *Optic Disc Edema* below, *Multiple Sclerosis*, N46

### Anterior Ischemic Optic Neuropathy

- see also *Optic Disc Edema*, below
- **non-arteritic (NAION)**: due to atherosclerosis
- **arteritic (AION)**: due to giant cell arteritis (see [Rheumatology](#), RH20)



If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results. Begin treatment immediately!



NAION can be caused by use of Sildenafil (Viagra®) in rare cases.

### Amaurosis Fugax

- see [Ophthalmology](#), OP37 and *Stroke*, N43



### Central Retinal Vein Occlusion (CRVO)

- see [Ophthalmology](#), OP24



### Optic Disc Edema

Table 5. Common Causes of Optic Disc Edema

	Optic Neuritis	Papilledema	AION	CRVO
<b>Age</b>	<50	Any	>50 but usually >70	>50
<b>Vision</b>	Rapidly progressive monocular central vision loss with ↓ acuity and colour vision with recovery	Late visual loss	Painless unilateral acute field defect over hours to days with ↓ colour vision	Painless unilateral variable vision loss
<b>Symptoms</b>	Pain (especially with eye movement)	Headache, n/v, local neurological deficits	If GCA: headache, scalp tenderness, jaw claudication, weight loss, fatigue	Cardiovascular risk factors
<b>Pupil</b>	RAPD	No RAPD	RAPD	± RAPD

**Table 5. Common Causes of Optic Disc Edema (continued)**

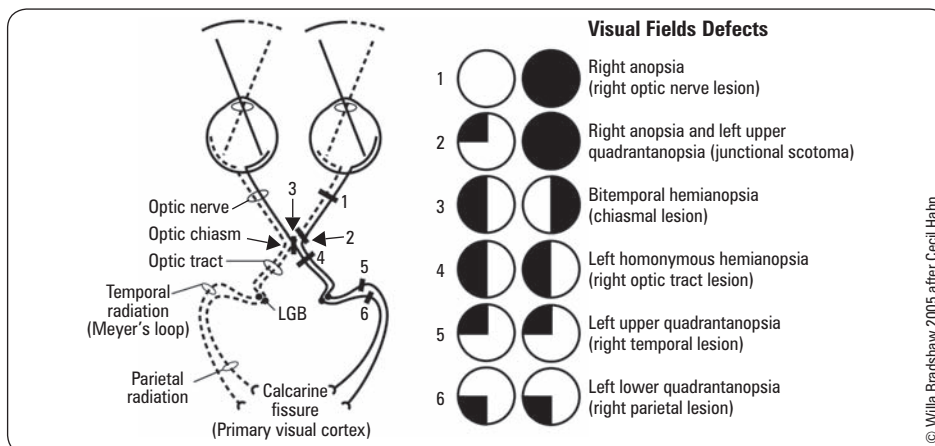
	Optic Neuritis	Papilledema	AION	CRVO
<b>Fundus</b>	Disc swelling if anterior Normal disc if retrobulbar	Bilateral disc swelling, retinal hemorrhage, no venous pulsations	Pale segmental disc edema, retinal dot, flame hemorrhages	Swollen disc, venous engorgement, retinal hemorrhage
<b>Etiologies</b>	MS, viral	Increased ICP	Giant cell arteritis Non-arteritic: atherosclerosis	Associated with vasculopathy, thrombus
<b>Investigations</b>	MRI with gadolinium	Emergent CT; LP if CT is normal to measure opening pressure	CBC, ESR, CRP, temporal artery biopsy	Fluorescein angiogram and coherence tomography
<b>Treatment</b>	IV methylprednisolone	Treat cause	Consider ASA if non-arteritic; steroids if arteritic	Optimize risk factors, reduce IOP, $\pm$ laser, $\pm$ VEGF inhibitors

## Optic Disc Atrophy

- **etiologies:** glaucoma, AION, compressive tumour, optic neuritis, Leber's hereditary optic neuropathy, congenital
- **presentation:** disc pallor, low visual acuity, peripheral vision defect, decreased colour vision
- **treatment:** none (irreversible), aim to prevent



## Abnormalities of Visual Field

**Figure 13. Characteristic visual field defects with lesions along the visual pathway**

### Bitemporal Hemianopsia DDX by Age

- Children: craniopharyngioma
- Middle aged (20s to 50s): pituitary mass
- Elderly (>60 yr): meningioma



In homonymous hemianopsia, more congruent deficits are caused by more posterior lesions. Macular sparing may occur with occipital lesions.



Check all hemiplegic patients for homonymous hemianopsia (ipsilateral to side of hemiplegia).

## Abnormalities of Eye Movements

### Disorders of Gaze

#### Pathophysiology

- horizontal gaze: FEF  $\rightarrow$  contralateral PPRF (midbrain/pons)  $\rightarrow$  eyes saccade away from FEF
- vertical gaze: cortex  $\rightarrow$  rostral interstitial nucleus in the MLF (midbrain)

#### Clinical Features

- unilateral lesion in one FEF  $\rightarrow$  eyes deviate toward the side of the lesion
  - can be overcome with doll's eye maneuver
- unilateral lesion in the PPRF  $\rightarrow$  eyes deviate away from the lesion
  - cannot be overcome with doll's eye maneuver if CN VI nucleus lesion as well
- seizure involving a FEF: eyes deviate away from the focus

#### Etiology

- common: infarcts (frontal or brainstem), MS, tumours



A lesion in a cerebral hemisphere causes eyes to "look away" from the hemiplegia, and to look towards the lesion.

A lesion in the brainstem causes the eyes to "look toward" the side of the hemiplegia, and to look away from the lesion.

## Internuclear Ophthalmoplegia (INO)



### Pathophysiology

- results from a lesion in MLF which disrupts coordination between CN VI nucleus in pons and the contralateral CNIII nucleus in midbrain → disrupts conjugate horizontal gaze

### Clinical Features

- horizontal diplopia on lateral gaze, oscillopsia
- on gaze away from the side of the lesion (see Figure 14)
  - ipsilateral adduction defect
  - contralateral abduction nystagmus
- cannot be overcome by caloric testing
- accommodation reflex intact
- may be bilateral (especially in MS)

### Etiology

- common: MS, brain stem infarct

### Investigations

- MRI

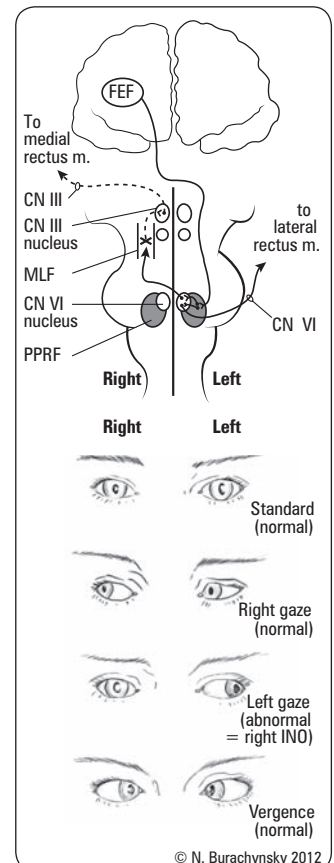


Figure 14. Internuclear ophthalmoplegia



Diplopia worse at the end of the day suggests myasthenia gravis (e.g. fatiguable).



If CN deficit is causing diplopia, it is worst in the direction of action of the muscle, but if restriction/entrapment is the cause, then diplopia is worst when trying to stretch the muscle (opposite direction).



If diplopia is only on extremes of gaze, cover each eye in isolation during extremes of gaze.

The covered eye that makes the lateral image disappear is the pathological one.

## Diplopia



### Etiology – Monocular

- mostly due to relatively benign optical problems (refractive error, cataract) or functional

### Etiology – Binocular (due to ocular misalignment)

- muscle
  - Graves' ophthalmopathy
  - EOM restriction/entrapment
- neuromuscular junction
  - MG (see *Myasthenia Gravis*, N32)
- cranial nerve palsy (see *Cranial Nerve Deficits*, N8)
- INO (see *Intranuclear Ophthalmoplegia*, above)
- other
  - orbital trauma (orbital floor fracture), tumour, infection, inflammation
  - Miller-Fisher variant of GBS
  - Wernicke's encephalopathy
  - leptomeningial disease

### Approach to Diplopia

- monocular vs. binocular
- horizontal vs. vertical vs. oblique diplopia
- direction of gaze that exacerbates diplopia
- corrective head movements

### Workup

- may observe isolated 4th or 6th nerve palsy for a few weeks, but workup if persistent or other symptoms develop
- indications for neuroimaging:
  - bilateral or multiple nerve involvement
  - severe sudden onset headache (rule out aneurysm)

## Nystagmus

- **definition:** rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
- direction of nystagmus is labelled by the **rapid** component of the eye movement
- can be categorized by movement type (pendular, jerking, rotatory, coarse) or as physiological vs. pathological

Table 6. Nystagmus Features

	Peripheral (vestibular)	Central (brainstem)
Direction	Unidirectional, fast phase away from the lesion	May be bilateral/unidirectional
Vertical nystagmus	–	±
Gaze fixation	Relieves nystagmus	Does not relieve nystagmus
Vertigo	Severe	Mild
Auditory symptoms	Common	Extremely rare
Other neurological signs	Absent	Often present
DDx	Benign paroxysmal positional vertigo, vestibular neuritis, Ménière disease, toxicity, trauma, Ramsay Hunt syndrome	MS, Vascular (brainstem/cerebellar), neoplastic/paraneoplastic

## Abnormalities of Pupils

- see [Ophthalmology](#), OP30

## Seizure Disorders and Epilepsy



### Seizure

#### Definitions

- seizure**: transient neurological dysfunction caused by excessive activity of cortical neurons, resulting in paroxysmal alteration of behaviour and/or EEG changes
- epilepsy**: chronic condition characterized by two or more unprovoked seizures

#### Classification

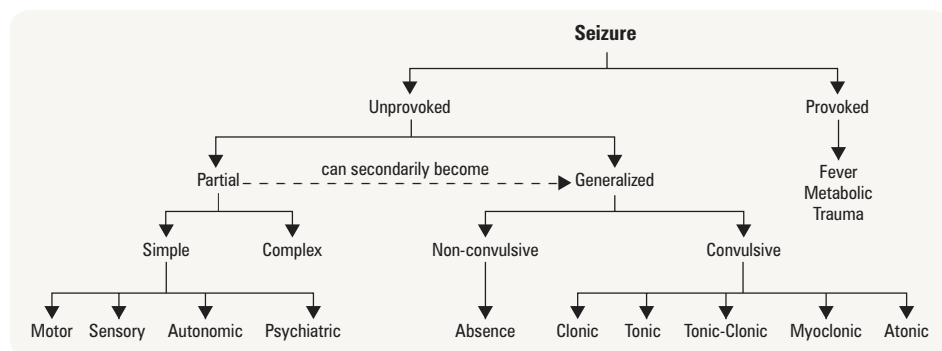


Figure 16. Classification of seizures

NOTE: seizures can also be classified using age of onset [childhood/adolescence, adulthood/late (i.e. >age 30)], setting (sleep, upon awakening), EEG (focal, generalized)

#### Signs and Symptoms

- generalized seizures (decreased LOC)**
  - tonic-clonic** [grand mal, generalized tonic-clonic (GTC)]:
    - ♦ prodrome of unease or irritability hours to days before the episode
    - ♦ tonic ictal phase: muscle rigidity
    - ♦ clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence
    - ♦ post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours
  - absence (petit mal)**: usually only seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - tonic**: muscle rigidity in flexion or extension
  - clonic**: repetitive rhythmic jerking movements
  - myoclonic**: sporadic contractions localized to muscle groups of one or more extremities
  - atonic**: loss of muscle tone leading to drop attack

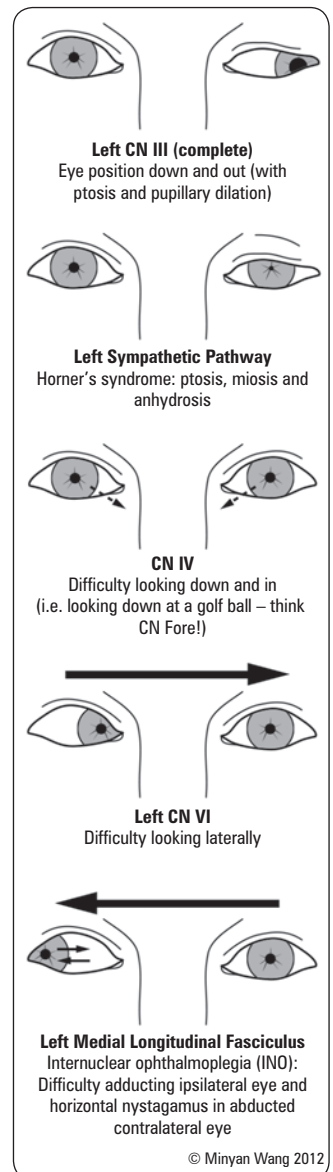


Figure 15. Abnormal eye movements



**Medical Emergency!** Status epilepticus can cause irreversible brain damage without treatment.



Stroke is the most common cause of late-onset (>50 yr of age) seizures, accounting for 50-80% of cases.



**Seizures and Dementia**  
Neurodegenerative diseases can underlie seizures. Conversely, seizures can be a cause of dementia.

- **partial seizures**

- simple or complex can secondarily generalize, or simple → complex → generalized seizures
- **simple (preserved LOC)**
  - ♦ motor: postural, phonatory, forceful turning of eyes and/or head, focal muscle rigidity/jerking ± Jacksonian march (spreading to adjacent muscle groups)
  - ♦ sensory: unusual sensations affecting vision, hearing, smell, taste or touch
  - ♦ autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
  - ♦ psychiatric: symptoms rarely occur without impairment of consciousness and are more commonly complex partial
- **complex (altered LOC)**
  - ♦ patient may appear to be awake but with impairment of awareness
  - ♦ classic complex seizure is characterized by automatisms such as chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing and other stereotypic movements
  - ♦ other forms: dysphasic, dysmnestic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness



Complex partial status epilepticus can resemble schizophrenia or psychotic depression.



Temporal lobe epilepsy is suggested by an aura of fear, olfactory or gustatory hallucinations and visceral or déjà vu sensations.

Frontoparietal cortex seizures are suggested by contralateral focal sensory or motor phenomena.

**Table 7. Classic Factors Differentiating Seizure versus Syncope**

Characteristic	Seizure	Syncope
Time of Onset	Day or night	Day
Position	Any	Upright, not recumbent
Onset	Sudden or brief	Gradual
Aura	Possible specific aura	Lightheaded sensation
Colour	Normal or cyanotic	Pallor
Autonomic	Uncommon outside of ictal phase	Common; diaphoresis
Duration	Brief or prolonged	Brief
Incontinence	Common	Possible but rare
Post-ictal	Occurs in tonic-clonic or complex partial	No
Motor Activity	Common	Occasional brief jerks
Injury	Common, tongue biting	Rare unless from fall
Automatisms	Common in absence or complex partial	None
EEG	Usually abnormal	Normal



#### DDx of Convulsions

Syncope, pseudoseizure, hyperventilation, panic disorder, TIA, hypoglycemia, movement disorder, alcoholic blackouts, migraines (confusional, vertebrobasilar), narcolepsy (cataplexy).



Note that frontal seizures (rare) can look like a pseudoseizure due to odd motor activity that may occur.

**Table 8. Classic Factors Differentiating Seizure versus Pseudoseizure (Conversion Disorder)**

Characteristic	Seizure	Pseudoseizure*
Triggers	Uncommon	Emotional disturbance
Duration	Brief or prolonged	May be prolonged
Motor Activity	Synchronous, stereotypic, automatisms, lateral tongue biting, eyes rolled back	Opisthotonos, rigidity, forced eye closure, irregular extremity movements, shaking head, pelvic thrust, crying, geotropic eye movements, tongue biting at the tip
Timing	Day or night	Day; other people present
Physical Injury	May occur	Rare
Incontinence	May occur	Rare
Reproduction of Attack	Spontaneous	Suggestion ± stimulus
EEG	Often inter-ictal discharges	Normal
Prolactin	Increased	Normal

\*Pseudoseizures do not rule out seizures (not uncommon to present with both)



By law, the Ministry of Transportation must be contacted for all patients who have had a seizure. Patients will have their license suspended until seizure free for 6 mo. Commercial drivers face a longer wait.

## Investigations

- CBC, electrolytes, fasting blood glucose,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , ESR, Cr, liver enzymes, CK, prolactin
- also consider toxicology screen, EtOH level, AED level (if applicable)
- CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
- LP (if fever or meningismus)
- EEG



## Treatment

- avoid precipitating factors
- indications for medical therapy (anticonvulsants): 2 or more unprovoked seizures, known organic brain disease, EEG with epileptiform activity, first episode of status epilepticus, abnormal neurologic examination or findings on neuroimaging
- psychosocial issues: stigma of seizures, education of patient and family, status of driver's license, pregnancy issues
- safety issues: driving, operating heavy machinery, bathing, swimming alone
- consider surgical treatment if focal and refractory

## Status Epilepticus

- **definition:** unremitting seizure of greater than 5 min; or successive seizures without return to a baseline state
- **complications:** anoxia, cerebral ischemia and cerebral edema, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)
- **initial measures:** ABCs, vitals, monitors, fingerprick glucose (STAT), ECG, nasal O<sub>2</sub>, IV NS, IV glucose, IV thiamine, ABGs (if respiratory distress/cyanotic)
- **bloodwork:** electrolytes, Ca<sup>2+</sup>, Mg<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup>, glucose, CBC, toxicology screen, EtOH level, AED levels
- **focused history:** onset, past history of seizures, drug and alcohol ingestion, past medical history, associated symptoms, witnesses/collateral history
- **physical exam** (once seizures controlled): LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (r/o injuries)

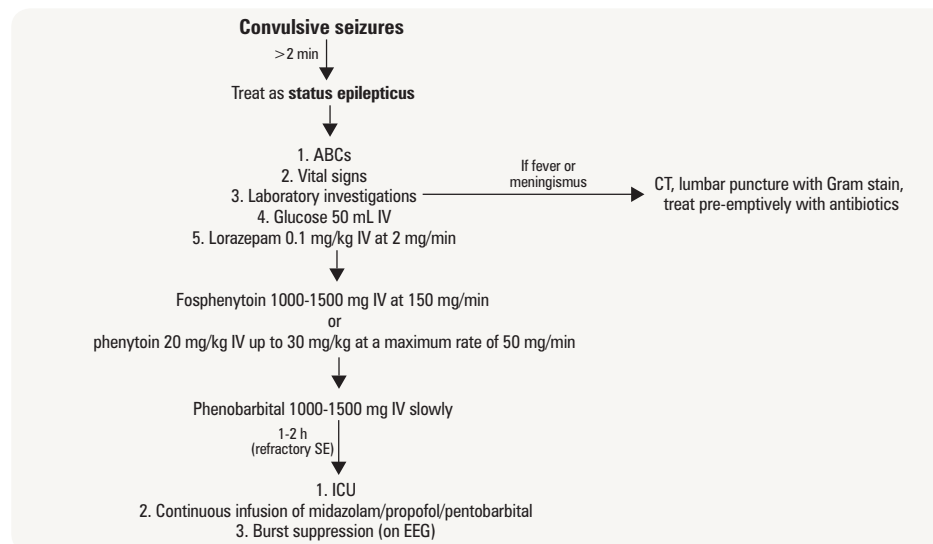


Figure 17. Status epilepticus treatment algorithm

## Antiepileptic Drugs (AED)

- **generalized-onset and partial-onset seizures:** felbamate, lamotrigine, levetiracetam, rifinamide, topiramate, valproate, zonisamide
- **partial seizures** (simple partial, complex partial and secondarily generalized seizures): carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, vigabatrin (note: these drugs may exacerbate generalized seizures)
- **absence seizures:** ethosuximide



### Pregnancy Issues

Teratogenicity of anticonvulsants includes neural tube defects, cleft palate, urogenital malformations and heart defects. Advise patient planning pregnancy to take 5 mg/d of folic acid. Optimize AEDs with lowest possible dose associated with good seizure control, preferably monotherapy if possible. Risk of fetal malformations with AEDs is 2x general population; highest risk associated with valproic acid and/or 2+ concurrent AEDs. Consider pre-conception AED levels if patient is well-controlled, monthly serum levels during pregnancy and titrate AED to maintain pre-conception serum levels. Refer to high risk OB for intrapartum fetal screening.



EEG findings suggestive of epilepsy: abnormal spikes, polyspike discharges, spike-wave complexes.



20-59% of first EEG are positive in epilepsy; 59-92% of epilepsy is picked up with repeated EEGs. Normal interictal EEGs do not rule out epilepsy.



The most common causes of status epilepticus are failure to take AEDs and first presentation of epilepsy. Status epilepticus as a result of EtOH withdrawal is rare, despite it being a very common cause of seizures.



Rule out non-convulsive status epilepticus in any patient who is still unconscious > 20 min post-ictal. Order a stat EEG if unsure.

# Behavioural Neurology

- see [Psychiatry](#), PS19



## Acute Confusional State/Delirium

**Table 9. Selected Intracranial Causes of Acute Confusion**

	Etiology	Key Clinical Features	Investigations
<b>Vascular</b>	Subarachnoid hemorrhage	Thunderclap headache Increased ICP Meningismus	CT (non-contrast) LP Angiography if CT, LP negative
	Stroke/TIA	Focal neurological signs	CT (non-contrast)
<b>Infectious</b>	Meningitis	Fever, headache, nausea, photophobia Meningismus	CT, LP
	Encephalitis	Focal neurological signs Fever, headache, $\pm$ seizure	CT, LP MRI
	Abscess	Increased ICP Focal neurological signs	CT with contrast (often ring enhancing lesion)
<b>Traumatic</b>	Diffuse axonal shear, epidural hematoma, subdural hematoma	Trauma hx Increased ICP Focal neurological signs	CT (non-contrast) MRI
<b>Autoimmune</b>	Acute CNS vasculitis Systemic Lupus Erythematosis	Skin rash, active joints	ANA, ANCA, RF MRI Angiography
<b>Neoplastic</b>	Mass effect/edema, hemorrhage, seizure	Increased ICP Focal neurological signs Papilledema	CT (non-contrast) MRI
<b>Seizure</b>	Status epilepticus	See <i>Seizure Disorders and Epilepsy</i> , N14	EEG
<b>Primary Psychiatric</b>	Psychotic disorder, mood disorder, anxiety disorder	No organic signs or symptoms	No specific tests



Delirium is a medical emergency carrying significant risk of morbidity and mortality. It is characterized by acute onset, disorientation, fluctuating level of consciousness, poor attention, and marked psychomotor changes.



Visual hallucinations more commonly indicate organic disease.

## Dementia

- see [Psychiatry](#), PS20

### Definition

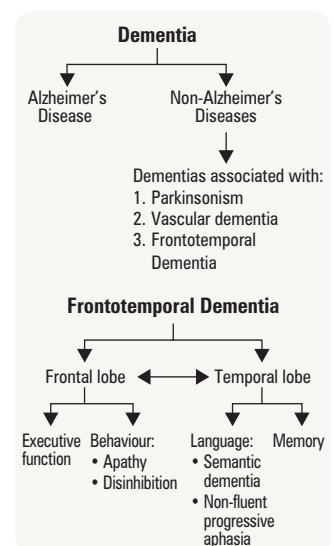
- an acquired, generalized and (usually) progressive impairment of cognitive function (i.e. memory, recall, orientation, language, abstraction) associated with impairment in activities of daily living (i.e. planning, shopping, food preparation, difficulties with finances)
- effect on content, but not level of consciousness
- see [Psychiatry](#), PS20 for DSM-IV diagnostic criteria
- see [Geriatric Medicine](#), GM5
- differentiated from Mild Cognitive Impairment (MCI) by the extent to which the impairment affects ADLs
  - MCI represents an intermediate stage between dementia and normal aging
  - by definition, IADLs are not affected in MCI

### Epidemiology

- 15% of those >65 yr of age have dementia
- <5% reversible

### Etiology

- see Table 10 for common causes of dementia
- see Table 11 for acquired causes of dementia
- reversible causes: alcohol (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metals toxicity, hepatic or renal failure, Wilson's disease, B<sub>12</sub> deficiency,  $\uparrow/\downarrow$  glucose,  $\uparrow/\downarrow$  cortisol, thyroid dysfunction, normal pressure hydrocephalus, depression (pseudodementia), intracranial tumour, subdural hematoma
- must rule out delirium



**Figure 18. Dementia classification**

## History

- “geriatric giants”
  - confusion/incontinence/falls/polypharmacy
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects)
  - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS
- alcohol, smoking
- OTCs, herbal remedies, medications (sedative hypnotics, antipsychotics, antidepressants, anticholinergics), compliance, accessibility
- history of vascular disease or head trauma
- collateral history

## Physical Examination

- blood pressure
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings, cerebrovascular disease
- general physical exam depending on risk factors and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

## Investigations

- depends on suspected etiologies (see Tables 10 and 11)
  - CBC (note MCV for evidence of alcohol use and B<sub>12</sub> deficiency), glucose, TSH, B<sub>12</sub>, RBC folate
  - electrolytes, LFTs, renal function, lipids, serum calcium
  - CT head, MRI as indicated, SPECT – optional
  - as clinically indicated: VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
  - failure to cope, fitness to drive, caregiver education and stress, power of attorney, legal will, advanced medical directives

**Table 10. Common Causes of Dementia**

Etiology	Key Clinical Features	Investigations
<b>PRIMARY DEGENERATIVE</b>		
Alzheimer's disease	Memory impairment Aphasia, apraxia, agnosia	CT or MRI, SPECT
Dementia with Lewy bodies	Visual hallucinations Parkinsonism Fluctuating cognition	CT or MRI, SPECT
Frontotemporal dementia (e.g. Pick's disease)	<u>Behavioural presentation</u> : Disinhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared <u>Language presentation</u> : Progressive non-fluent aphasia, semantic dementia	CT or MRI, SPECT
Huntington's disease	Chorea	Genetic testing
<b>VASCULAR</b>		
Multi-infarct dementia	May be abrupt onset Stepwise deterioration is classic but progressive deterioration is most common Dysexecutive syndrome Focal neurological findings	CT or MRI, SPECT
CNS vasculitis	Systemic S&S of vasculitis	ANA; ANCA; RF CT or MRI Angiography

**Table 11. Acquired Causes of Dementia**

Etiology	Key Clinical Features	Investigations
<b>INFECTIOUS</b>		
Chronic meningitis	Fever, headache, nausea Meningismus Localizing neuro deficits	CT, LP
Chronic encephalitis	Fever, headache	CT or MRI
Chronic abscess	Increased ICP Localizing neuro signs	CT with contrast
HIV	See <a href="#">Infectious Diseases</a> , ID41	HIV serology
Creutzfeldt-Jacob disease	Rapidly progressive, myoclonus	EEG, CT or MRI, LP
Syphilis	Ataxia, myoclonus, tabes dorsalis	LP, CT or MRI VDRL



### Sensitivity and Specificity

Tool	Sensitivity	Specificity
MMSE	87%	82%
Clinical Judgment	85%	82%
DSM IV	76%	80%



### Vitamin B<sub>12</sub> Deficiency Symptoms

- Macrocytic anemia, pallor, SOB, fatigue, chest pain, palpitations
- Confusion or change in mental status (if advanced)
- Decreased vibration sense
- Distal numbness and paresthesia
- Weakness with UMN findings
- Diarrhea, anorexia



### Dementia DDX

#### VITAMIN D VEST

- Vitamin deficiency (B<sub>12</sub>, folate, thiamine)
- Intracranial tumour
- Trauma (head injury)
- Anoxia
- Metabolic (diabetes)
- Infection (postencephalitis, HIV)
- Normal pressure hydrocephalus
- Degenerative (Alzheimer's, Huntington's, CJD)
- Vascular (multi-infarct dementia)
- Endocrine (hypothyroid)
- Space occupying lesion (chronic subdural hematoma)
- Toxic (alcohol)



Most common causes of rapidly progressive neurodegenerative dementia (less than 4 yr survival): CJD, frontal temporal lobar dementia, tauopathies, diffuse Lewy body disease and AD.

*Arch Neurol* 2009;66:201-207




### Dementia Considerations for Management

#### ABCDs

- Affective disorders and ADLs
- Behavioural problems
- Caretaker, cognitive medications and stimulation
- Directives, Driving
- Sensory enhancement (glasses/hearing aids)



**Table 11. Acquired Causes of Dementia** (continued)

Etiology	Key Clinical Features	Investigations
<b>TRAUMATIC</b>		
Diffuse axonal shear, epidural hematoma, subdural hematoma	Trauma Hx Increased ICP, papilledema Localizing neuro signs	CT (non-contrast)
<b>RHEUMATOLOGIC</b>		
SLE	See <a href="#">Rheumatology</a> , RH11 	MRI ANA, anti-dsDNA
<b>NEOPLASTIC</b>		
Mass effect/edema, hemorrhage, seizure Paraneoplastic encephalitis	Increased ICP Localizing neuro signs Systemic symptoms of cancer	CT with contrast MRI Anti-Hu antibodies



**Cholinesterase Inhibitors for Dementia with Lewy bodies (DLB), Parkinson's Disease Dementia (PDD) and Cognitive Impairment in Parkinson's Disease (CIND-PD)**

*Cochrane DB Syst Rev 2012;3:CD006504*

**Study:** Meta-analysis of RCTs assessing efficacy of treatment with cholinesterase inhibitors in DLB, PDD, and CIND-PD.

**Results:** The six trials (n=1236) included demonstrated therapeutic benefit of cholinesterase inhibitor for global assessment, cognitive function, behavioural disturbance, and activities of daily living. Cholinesterase Inhibitor was associated with increased adverse events (OR 1.64) and drop out (OR 1.94). Adverse events were more common with rivastigmine but not with donepezil. Fewer deaths occurred in the treatment group (OR 0.28).

**Conclusion:** Current evidence supports use of cholinesterase Inhibitors for patients with PDD but its role in DLB and CIND-PD is still unclear.

## Alzheimer's Disease (AD)

- see [Psychiatry](#), PS20 

### Definition

- progressive cognitive decline interfering with social and occupational functioning characterized by the following
  1. anterograde amnesia: impaired ability to learn new information
  2. one of the following cognitive disturbances
    - a. aphasia: language disturbance
    - b. apraxia: impaired ability to carry out motor activities despite intact motor function
    - c. agnosia: failure to recognize or identify objects despite intact sensory function
    - d. disturbance in executive function: impaired planning, organizing, sequencing, abstracting

### Pathophysiology

- genetic factors
  - minority (<7%) of AD cases are familial (autosomal dominant)
  - 3 major genes for autosomal dominant AD have been identified:
    - ♦ amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
  - the E4 polymorphism of apolipoprotein E is a susceptibility genotype (E2 is protective)
- pathology (although not necessarily specific for AD)
  - gross pathology
    - ♦ diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  - microscopic pathology
    - ♦ senile plaques (extracellular deposits of amyloid in the grey matter of the brain)
    - ♦ loss of synapses
    - ♦ neurofibrillary tangles (intracytoplasmic paired helical filaments with  $\beta$ -amyloid and hyperphosphorylated Tau protein)
    - ♦ loss of cholinergic neurons in nucleus basalis of Meynert that project to the frontal cortex
  - biochemical pathology
    - ♦ 50-90% reduction in action of choline acetyltransferase

### Epidemiology

- 1/12 of population 65-75 yr of age
- 1/3 of population >85 yr of age
- accounts for 60-80% of all dementias

### Risk Factors

- age, family history, smoking, head injury, low education level, Down's syndrome

### Signs and Symptoms

- cognitive impairment
  - memory impairment for newly acquired information (early)
  - deficits in language, abstract reasoning and executive function
- psychiatric manifestations
  - major depressive disorder (5-8%)
  - psychosis (20%)
  - apathy
- motor manifestations (late)
  - parkinsonism (if present consider DLB)

### Investigations

- perform investigations to rule out other causes of dementia as necessary
- EEG: usually normal, may observe generalized slowing (nonspecific)
- MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
- SPECT: hypoperfusion in temporal and parietal lobes



#### 4 As and one D of AD

Anterograde amnesia

Aphasia

Apraxia

Agnosia

Disturbance in executive function

(Anterograde amnesia plus at least one of the other features is required for AD diagnosis)



Down's syndrome predisposes to early onset of Alzheimer's (i.e. age of ~40) due to three copies of the amyloid gene (APP)

### Treatment

- acetylcholinesterase inhibitors have been shown to slow decline in cognitive function
  - donepezil, rivastigmine, galantamine
  - relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers or risk factors for ulcers and GI bleeding
  - galantamine is contraindicated in patients with hepatic/renal impairment
- memantine is an NMDA-receptor antagonist that has some benefits in later stage AD (i.e. when MMSE <17)
- symptomatic management
  - pharmacologic
    - low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
    - trazodone for sleep disturbance
    - antidepressants (SSRIs)
  - non-pharmacologic
    - redirection
    - explore inciting factors for behaviour and modify behavior of patient or caregiver
    - family support and day care facilities

### Prognosis

- progressive with mean duration of disease 10 yr



#### Cognitive Effects of Atypical Antipsychotic Medications in Patients with Alzheimer's Disease: Outcomes from CATIE-AD

*Am J Psychiatry* 2011;168:831-839

**Study:** 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behaviour were randomized to receive olanzapine, quetiapine, risperidone, or placebo in a multicenter double-blinded RCT. MMSE and Alzheimer's Disease Assessment Scale (ADAS) scores were measured at 36 wk.

**Results:** Patients receiving atypical antipsychotics exhibited a faster rate of cognitive decline as measured by MMSE scores ( $-0.067/\text{wk}$  vs.  $-0.007/\text{wk}$ ). They also had a significantly faster decline compared to placebo on a composite measure of ADAS, MMSE and various other cognitive tests ( $-0.011/\text{wk}$  vs.  $-0.001/\text{wk}$ ).

**Conclusions:** Long-term use of atypical antipsychotics for behavioural symptoms and psychosis in dementia patients is associated with greater rates of cognitive decline.

## Dementia with Lewy Bodies (DLB)

### Definition

- progressive cognitive decline interfering with social or occupational function; memory loss usually not an early feature
- one (possible DLB) or two (probable DLB) of the following:
  - fluctuating cognition with pronounced variation in attention and alertness
  - recurrent visual hallucinations
  - parkinsonism (not to be confused with Parkinson's disease dementia)
  - suggestive or supportive features include REM sleep disorder, sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms), repeated falls (late disease)

### Etiology and Pathogenesis

- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
- mixed DLB and AD pathology is common

### Epidemiology

- 15-25% of all dementias

### Treatment

- acetylcholinesterase inhibitors (e.g. donepezil)

### Prognosis

- typical survival 3-6 yr

## Frontotemporal Dementia (FTD)

### Definition

- FTD is a progressive dementia; third most common cause of cortical dementia
- behavioural variant of FTD (more common) presents with social conduct disorder predominantly
- language variants:
  - progressive nonfluent aphasia: non-fluent, laboured articulation/speech, anomia, preserved single word comprehension, word-finding deficit, impaired repetition
  - semantic dementia: fluent, normal rate, anomia, impaired single word comprehension, intact repetition, use words of generalization ("thing") or supraordinate categories ("animal" for "dog")

### Etiology and Pathogenesis

- unknown, likely genetic/familial component
- two main histological types:
  - frontal lobe degeneration with microvacuolar change
  - Pick type with astrocytic gliosis  $\pm$  ballooned cells and inclusion bodies

### Epidemiology

- 10% of all dementias

## Signs and Symptoms

- diagnosis of behavioural variant of FTD:
  - core features:
    1. insidious onset and gradual progression
    2. early decline in social interpersonal conduct
    3. early impairment in regulation of personal conduct
    4. early emotional blunting
    5. early loss of insight
  - supportive features:
    1. behavioural (decline in personal hygiene, mental rigidity, distractibility, hyperorality, perseverative or utilization behaviour)
    2. speech and language (perseverative or stereotyped speech, echolalia, mutism)
    3. physical signs (primitive reflexes, incontinence, akinesia, rigidity, tremor, low and labile blood pressure)
- severe frontal lobe impairment in absence of severe amnesia, aphasia, perceptual disorder
- imaging: predominant frontal and/or anterior temporal atrophy
- EEG usually normal

## Creutzfeldt-Jakob Disease (CJD)

- rare degenerative fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
- most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)
- investigations: CSF analysis, MRI brain (cortical and/or subcortical FLAIR changes), EEG (periodic complexes)
- definitive diagnosis is by brain biopsy
- no treatments currently exist



Prion proteins have a normal form and an infectious form. The infectious form is abnormally folded and leads to abnormal folding of normal prion proteins. These abnormally folded proteins aggregate leading to neuronal loss.

## Normal Pressure Hydrocephalus

- see [Neurosurgery](#), NS8

## Aphasia

### Definition

- an acquired disturbance of language characterized by errors in speech production, writing, comprehension, or reading

### Neuroanatomy of Aphasia

- Broca's area (posterior inferior frontal lobe) involved in speech production (expressive)
- Wernicke's area (posterior superior temporal lobe) involved in comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke's area for reading comprehension
- arcuate fasciculus association bundle connects Wernicke's and Broca's areas

### Assessment of Language

- assessment of context
  - handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
- assessment of aphasia
  - spontaneous speech (fluency, paraphasias, repetition, naming, comprehension – auditory and reading, writing, neologisms)

Table 12. Approach to Aphasias

	Fluency	Comprehension	Repetition	Naming	Lesion Localization
<b>Broca's</b>	Non-fluent	Good	Poor	Poor	Posterior inferior frontal lobe
<b>Motor TCA*</b>	Non-fluent	Good	Good	Poor	Frontal lobe watershed between MCA and ACA territories
<b>Mixed TCA*</b>	Non-fluent	Poor	Good	Poor	Sensory and motor transcortical regions
<b>Global</b>	Non-fluent	Poor	Poor	Poor	Posterior inferior frontal lobe AND posterior superior temporal lobe
<b>Wernicke's</b>	Fluent	Poor	Poor	Relatively spared	Posterior superior temporal lobe
<b>Conduction</b>	Fluent	Good	Poor	Poor	Arcuate fasciculus
<b>Sensory TCA*</b>	Fluent	Poor	Good	Relatively spared	Temporoparietal watershed between MCA and PCA territories
<b>Anomic</b>	Fluent	Good	Good	Poor	Numerous possible locations

TCA=Transcortical aphasia

\*Transcortical aphasias are typically associated with cerebral anoxia (e.g. post-MI, CO poisoning, hypotension)

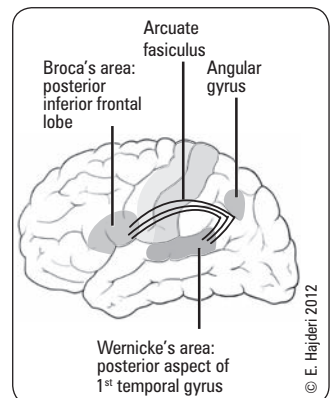


Figure 19. Broca's and Wernicke's areas



>99% of right-handed people have left hemisphere language representation. 70% of left-handed people have left hemisphere language representation, 15% have right hemisphere representation and 15% have bilateral representation.



### Types of Paraphasias

- Semantic ("chair" for "table")
- Phonemic ("clable" for "table")



Aphasia localizes the lesion to the dominant cerebral hemisphere.



## Apraxia

### Definition

- inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension or inattention

### Clinicopathological Correlations

Table 13. Apraxia

	Description	Tests	Hemispheres
<b>Ideomotor</b>	Inability to perform skilled learned motor sequences	Blowing out a match; combing one's hair	Left
<b>Ideational</b>	Inability to sequence actions	Preparing and mailing an envelope	Right and left
<b>Constructional*</b>	Inability to draw or construct	Copying a figure	Right and left
<b>Dressing*</b>	Inability to dress	Dressing	Right

\*Refers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks

## Agnosia

### Definition

- disorder in the recognition of the significance of sensory stimuli in the presence of intact sensation and naming

### Clinicopathological Correlations

Table 14. Agnosias

	Description	Lesion
<b>Aperceptive visual agnosia</b>	Inability to name or demonstrate the use of an object presented visually 2° to distorted visual perception Recognition by touch remains intact	Bilateral temporo-occipital cortex
<b>Associative visual agnosia</b>	Inability to name an object presented visually 2° to disconnect between visual cortex and language areas Visual perception is intact as demonstrated by visual matching	Bilateral inferior temporo-occipital junction
<b>Prosopagnosia</b>	Inability to recognize familiar faces in the presence of intact visual perception and intact auditory recognition	Bilateral occipitotemporal areas or right inferior temporo-occipital region
<b>Colour agnosia</b>	Inability to perceive colour	Bilateral inferior temporo-occipital lesions
<b>Astereognosis</b>	Inability to identify objects by touch	Anterior parietal lobe in the hemisphere opposite the affected hand
<b>Finger agnosia</b>	Inability to recognize, name, and point to individual fingers	Dominant hemisphere parietal-occipital lesions



#### Parietal Lobe Lesions

- Lesions of the dominant parietal lobe are characterized by Gerstmann's syndrome: acalculia, agraphia, finger agnosia, and left-right disorientation
- Lesions of the non-dominant parietal lobe are characterized by neglect, anosognosia, and asomatognosia
- Cortical sensory loss (graphesthesia, astereognosis, impaired 2 point discrimination and extinction) can be seen with left or right parietal lesions



- Extent of retrograde amnesia correlates with severity of injury
- Regained from most distant to recent memories



## Mild Traumatic Brain Injury

### Definition

- mild TBI = concussion
- trauma induced transient alteration in mental status that may involve loss of consciousness
- hallmarks of concussion: confusion and amnesia, which may occur within minutes
- loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15 and post-traumatic amnesia must be less than 24 h

### Epidemiology

- 75% of TBIs are estimated to be mild; remainder are moderate or severe (see [Neurosurgery](#), NS30 and [Emergency Medicine](#), ER7)
- highest rates in children 0-4 yr, adolescents 15-19 yr and elderly >65 yr

### Clinical Features

- impairments following mild TBI:
  - somatic: headache, sleep disturbance, nausea, vomiting, blurred vision
  - cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
  - emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
- associated conditions: brain contusion, diffuse axonal injury, C-spine injury

**Investigations**

- neuro exam to identify focal neurologic deficits
- neurocognitive assessment:
  - simple orientation questions are inadequate to detect cognitive changes
  - initial assessment of severity is determined by:
    - ♦ Glasgow Coma Scale: mild: 13-15, moderate: 9-12, severe: 3-8
  - sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool
- neuroimaging:
  - x-ray of skull: not indicated for routine evaluation of MTBI
  - CT head as indicated by Canadian CT Head Rules (see [Emergency Medicine](#), ER10)
  - MRI not indicated in initial evaluation – indicated in presence of continued or worsening symptoms despite normal CT

**Treatment**

- observation for first 24 h after mild TBI in all patients because of risk of intracranial complications
- emergency department for assessment if any loss of consciousness or persistent symptoms
- hospitalization if: with normal CT (GCS <15, seizures, bleeding diathesis), abnormal CT scan
- early rehabilitation to maximize outcomes
  - OT, PT, SLP, vestibular therapy, driving, therapeutic recreation
- pharmacological management of headaches, pain, depression
- cognitive behavioural therapy, relaxation therapy
- follow Return to Play guidelines ([www.thinkfirst.ca](http://www.thinkfirst.ca))

**Prognosis**

- most recover from mild TBI with minimal treatment, but some experience long-term consequences
- athletes with a previous concussion are at increased risk of subsequent concussion and cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
- sequelae include
  - postconcussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within weeks to months)
  - post-traumatic headaches: begin within seven days of injury
  - post-traumatic epilepsy: twofold increase in risk of epilepsy in 5 yr post TBI, prophylactic anticonvulsants not effective
  - post-traumatic vertigo

## Neuro-oncology

### Paraneoplastic Syndromes

- see [Endocrinology](#), E51



### Tumours of the Nervous System

- see [Neurosurgery](#), NS10



# Movement Disorders



## Overview of Movement Disorders

**Table 15. Movement Disorder Definitions**

<b>Akathisia</b>	Subjective restlessness relieved by stereotypic movements (e.g. squirming)
<b>Asterixis</b>	Loss of muscle contraction (negative myoclonus)
<b>Athetosis</b>	Slow writhing movements, especially distally
<b>Bradykinesia</b>	Slow and/or small amplitude movements
<b>Chorea</b>	Brief, abrupt, irregular movements; can appear purposeful in milder forms
<b>Dyskinesia</b>	Any sudden involuntary movement, but the term is often used to describe the stereotypical movements that come with long term neuroleptic or dopaminergic use
<b>Dystonia</b>	Co-contraction of agonist and antagonists causing sustained twisting movements
<b>Freezing</b>	Episodes of halted motor action, especially during walking
<b>Hemiballismus</b>	Unilateral violent flinging movement
<b>Myoclonus</b>	Brief muscle group contraction that is either focal, segmental, or generalized
<b>Myokimia</b>	Spontaneous, fine, fascicular contraction of muscle
<b>Tachykinesia</b>	Acceleration of movements
<b>Tics</b>	Stereotyped repetitive actions due to inner urge; can be suppressed
<b>Tremor</b>	Rhythmic alternating muscle contraction and relaxation



In some cases, dystonias may only occur during voluntary movement and sometimes only during specific activities such as writing, chewing, or speaking.



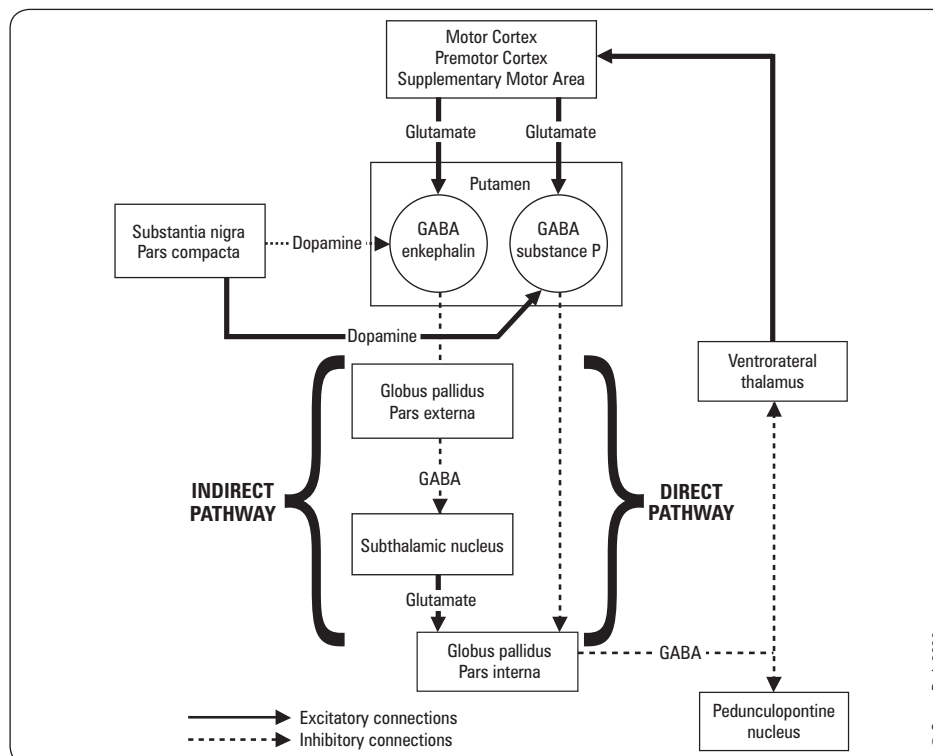
Hemiballismus is a prominent unilateral chorea that is most often due to a vascular lesion of the contralateral subthalamic nucleus.



Some myoclonus is stimulus sensitive and can be induced by noise, movement, light, visual threat or pinprick.

## Function of the Basal Ganglia

- the cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, which then activate two pathways: direct and indirect
- direct: cortex → striatum → GPi/SNr → thalamus → motor cortex
  - activation of this pathway removes the inhibitory effect of the GPi on the thalamus, letting the thalamus activate the cortex and ultimately allowing movement
- indirect: cortex → striatum → GPe → STN → GPi/SNr → thalamus → motor cortex
  - activation of this pathway causes inhibition of the thalamus and ultimately prevents movement



**Figure 20. Neural connections of the basal ganglia**

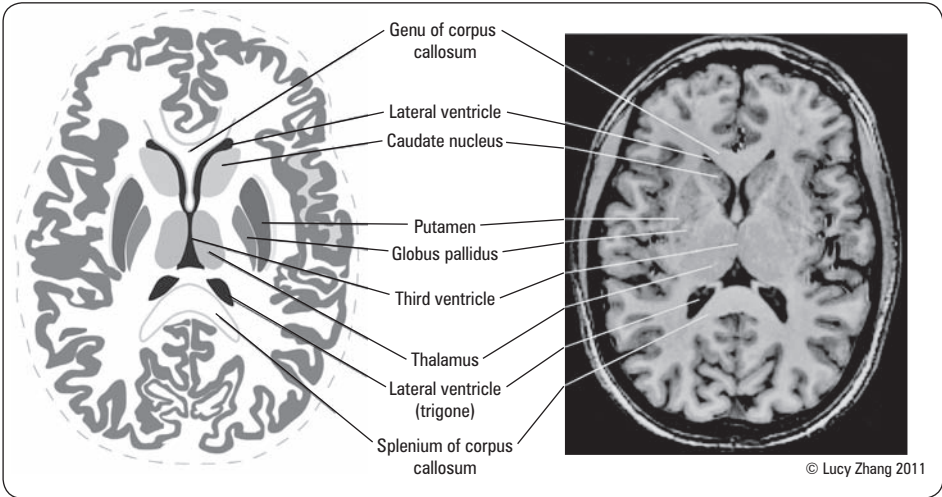


Figure 21. Horizontal section of basal ganglia

Movement Disorders

Differential Diagnoses

1. Tremor:

- **postural:** physiologic, anxiety, sedative/alcohol withdrawal, drug toxicity, heavy metal poisoning, carbon monoxide poisoning, thyrotoxicosis, benign essential tremor, cerebellar, Wilson's disease
  - ♦ benign essential tremor is a common autosomal dominant trait that presents as a bilateral postural tremor of the vertical axis, especially in the upper extremities
- **intention:** brainstem lesion, cerebellar lesion, alcohol, anticonvulsants, sedatives, Wilson's disease
- **resting:** Parkinsonism, Wilson's disease, mercury poisoning

Table 16. Approach to Tremors

	Resting	Postural	Intention
Body Part	Distal UE	UE/head/voice	Anywhere
Characteristics	3-7 Hz pill rolling	6-12 Hz fine tremor	< 5 Hz coarse tremor
Worse with	Rest while concentrating	Sustained posture (outstretched arms)	Finger to nose
Associated Sx	"TRAP"	± Autosomal dominant FHx	Cerebellar findings
DDx	PD, Parkinsonism, Wilson's disease	Physiologic, benign essential, drugs, hyperthyroid, hyperglycemic	Cerebellar disorders, Wilson's disease, alcohol, MS
Treatment	Sinemet, surgery, DBS	Propranolol, anticonvulsants, primidone	Treat underlying cause

2. **Chorea:** Huntington's disease, neuroacanthocytosis, SLE, APLA syndrome, Wilson's disease, cerebrovascular disease, tardive dyskinesia, senile chorea, Sydenham's chorea, pregnancy chorea

3. Dystonia

- **primary dystonia:** familial, sporadic (torticollis, blepharospasm, writer's cramp)
- **dystonia-plus syndromes:** dopa-responsive dystonia, myoclonus-dystonia
- **secondary dystonia:** thalamotomy, stroke, CNS tumour, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
- **heterodegenerative dystonias:** Parkinsonian disorders, Wilson's disease, Huntington's disease

4. Myoclonus

- **physiologic myoclonus:** hiccups, nocturnal myoclonus
- **essential myoclonus**
- **epileptic myoclonus**
- **symptomatic myoclonus:**
  - degenerative disorders (Wilson's disease, Huntington disease, Alzheimers)
  - infectious disorders (CJD, viral encephalitis, AIDS-dementia complex)
  - metabolic disorders (drug intoxication/withdrawal, hypoglycemia, hyponatremia, HONK, hepatic encephalopathy, uremia, hypoxia)
  - focal brain damage (head injury, stroke, mass)



In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson's disease), and CT/MRI (cerebellar disease) as indicated by type of tremor.



**Alcohol**

- Dampens essential tremor
- Potentiates intention tremor
- Does not improve resting tremor of PD



> 90% of essential tremor does not need treatment.



Most common cause of chorea is drug therapy for PD.



**Palatal myoclonus** can result from lesion to the dentatorubroolivary pathway, and is associated with an audible clicking.

## 5. Tics

- **primary tic disorders:** transient tic disorder, chronic tic disorder, Gilles de la Tourette, adult onset or senile
- **secondary tic disorders:** encephalitis, CJD, Sydenham's chorea, head trauma, drugs, mental retardation syndromes
- association with OCD and ADHD

## Parkinson's Disease (PD)

### Etiology

- **sporadic:** combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- **familial** (10%): autosomal dominant  $\alpha$ -synuclein mutations, autosomal recessive Parkin gene or DJ-1 gene mutation (juvenile onset)
- **MPTP** (neurotoxin)

### Epidemiology

- prevalence of 0.3% in industrialized countries, but rises with increased age
- second most common neuro-degenerative disorder, after Alzheimer's
- mean age of onset is 60 yr

### Risk Factors

- family history, male, head injury, rural living, exposure to certain neuro toxins
- protective: coffee drinking, smoking, NSAID use, estrogen replacement in post-menopausal women

### Pathophysiology

- loss of dopaminergic neurons in pars compacta of substantia nigra, thus reduced dopamine in striatum leading to disinhibition of the indirect pathway and decreased activation of the direct pathway causing increased inhibition of cortical motor areas
- $\alpha$ -synucleinopathy:  $\alpha$ -synuclein accumulates in Lewy bodies and causes neurotoxicity in substantia nigra

### Signs and Symptoms

- positive motor
  - resting tremor: asymmetric 4-5Hz "pill-rolling" tremor, especially in hands
  - rigidity: lead-pipe rigidity with cogwheeling due to superimposed tremor
- negative motor
  - bradykinesia: slow small amplitude movements, fatiguing of rapid alternating movements, difficulty initiating movement
- related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
- freezing: occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds
- postural instability: late finding presenting as falls, festinating gait
- cognition: bradyphrenia (slow to think/respond), dementia (late finding)
- behavioural: decreased spontaneous speech, depression, sleep disturbances, anxiety
- autonomic: constipation, urinary retention, sexual dysfunction, later findings of orthostatic hypotension

### Treatment

- pharmacologic
  - mainstay of treatment: Sinemet® (levodopa/carbidopa). Levodopa is a dopamine precursor; carbidopa decreases peripheral metabolism of levodopa, decreasing side effects and increasing half-life of levodopa
    - ♦ levodopa related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration ("wearing-off"), random oscillations of on-off symptoms
    - ♦ major complication of levodopa is dyskinesia
  - treatment of early PD: dopamine agonists, amantadine, MAOI
  - adjuncts: dopamine agonists, MAOI, anticholinergics (especially if prominent tremors), COMT inhibitors
- surgical: thalamotomy, pallidotomy, DBS (thalamic, pallidal, subthalamic), embryonic dopaminergic stem cell transplantation
- psychiatric (see [Psychiatry](#), PS21)



#### Key Parkinsonian Features

##### TRAP

Tremor (resting)  
Rigidity  
Akinesia/bradykinesia  
Postural instability



#### Diagnostic Criteria:

- Bradykinesia, plus one of: resting tremor, muscle rigidity, postural instability not caused by other factors, or
- 3 or more of the following features:
  - Resting tremor
  - Unilateral onset
  - Persistent asymmetry, with side of onset most affected
  - Progressive disorder
  - Excellent response (70-100%) to levodopa
  - Severe levodopa-induced chorea
  - Response to levodopa for 5 or more years
  - Clinical course lasting 10 or more years



#### Consider an Alternative Diagnosis if Atypical Parkinsonism

- Poor response to L-dopa
- Abrupt onset of symptoms
- Rapid progression
- Early falls
- Early autonomic dysfunction
- Symmetric symptoms at onset
- Early age of onset (<50)
- Early cognitive impairment
- FHx of psychiatric/dementing disorders
- Recent diagnosis of psychiatric disease
- History of encephalitis
- Unusual toxin exposure
- Extensive travel history



#### Dopamine Agonist Therapy in Early Parkinson's Disease

Cochrane DB Syst Rev 2009;2:CD006564

**Study:** Meta-analysis of trials of dopamine agonists in early Parkinson's disease.

**Results:** Twenty-nine trials were included (n=5247). Dopamine agonists were found to have decreased motor side effects [dyskinesia (OR 0.51), dystonia (OR 0.64), motor fluctuations (OR 0.75)] compared to levodopa, but provided poorer symptom control compared to levodopa. Also, other side effects were increased [constipation (OR 1.59), hallucinations (OR 1.69), dizziness (OR 1.45)].

**Conclusion:** Dopamine agonists have fewer motor side effects than levodopa, but provide worse symptom control and increased rate of other side effects.

## Other Parkinsonian Disorders

- **dementia with Lewy bodies** (see *Behavioural Neurology*, N20)
- **progressive supranuclear palsy**: tauopathy with limited vertical gaze (classically downgaze), early falls, axial rigidity and akinesia, dysarthria and dysphagia
- **corticobasal degeneration**: tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia ± “alien limbs” phenomenon
- **multiple system atrophy**: synucleinopathy presenting as either cerebellar predominant (previously olivo-ponto cerebellar atrophy or OPCA) or parkinsonism predominant (previously striato-nigral degeneration). Both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- **vascular parkinsonism**: multi-infarct presentation with lower body parkinsonism

## Huntington's Disease

### Etiology and Pathogenesis

- genetics: autosomal dominant CAG repeats (with anticipation) in Huntington gene on Chromosome 4, which leads to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway and decreased activity of the indirect pathway

### Epidemiology

- North American prevalence 4-8/100,000
- mean age of onset 35-44 yr; but varies with degree of anticipation from 5-70

### Signs and Symptoms

- typical progression: insidious onset with clumsiness, fidgetiness and irritability, progressing over 15 yr to frank dementia, psychosis and chorea
  - dementia: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudopurposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence

### Investigations

- MRI: enlarged ventricles, atrophy of cerebral cortex and caudate nucleus
- genetic testing
  - expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene
  - CAG repeats on chromosome 4p16.3 that encodes the protein huntingtin

### Treatment

- no disease altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin



**Juvenile Onset (Westphal variant):**  
Begins in adolescence with bradykinesia and rigidity with a severe progressive course spanning 5-10 yr.

## Dystonia

### Epidemiology

- second most common movement disorder, after parkinsonism

### Clinical Features

- symptoms exacerbated by fatigue, stress, emotions; relieved by sleep or specific tactile/proprioceptive stimuli ('geste antagonist', e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalize if younger onset or leg dystonia

### Treatment

- local medical: botulinum toxin
- systemic medical: anticholinergics (benztropine), muscle relaxants (baclofen), benzodiazepines, antidopaminergics (reserpine, neuroleptics); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotaxic thalamotomy (unilateral dystonia), posteroventral pallidotomy



Botulinum toxin (BOTOX®) acts by preventing ACh release at the neuromuscular junction.



## Tic Disorders

### Clinical Classification

- **motor tics**
  - **simple:** blinking, head jerking
  - **dystonic:** bruxism, grinding teeth, abdominal tension, sustained mouth opening
  - **complex:** copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- **vocal tics**
  - **simple:** blowing, coughing, grunting, throat clearing
  - **complex:** coprolalia (shout obscenities), echolalia (repeat others' phrases), palilalia (repeat own phrases)

### Treatment

- dopamine blocker

## Tourette's Syndrome (aka Gilles de la Tourette's Syndrome)

### Definition according to DSM IV

1. Presence of motor and vocal tics at some point during illness, not necessarily concurrently
2. Multiple tics a day nearly everyday or intermittently throughout 1 yr with no tic-free periods greater than 3 mo
3. Onset prior to 18 yr of age
4. Not due to effect of a substance or general medical condition

### Epidemiology

- prevalence among adolescents 3-5/100,000; M>F

### Signs and Symptoms

- tics: wide variety that wax and wane in type and severity
  - can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
- psychiatric: compulsive behaviours (associated with OCD and ADHD), hyperactive behaviour, 'rages', sleep-wake disturbances, learning disabilities

### Treatment

- clonidine, clonazepam

### Prognosis

- begins at 5 yr of age progressively increasing until 10 yr; often improves in adolescence and 50% are tic-free by 18 yr of age



Less than 15% of people with Tourette's have coprolalia.

## Cerebellar Disorders

### Clinico-Anatomic Correlations

- **vermis:** trunk/gait ataxia
- **cerebellar lobe (i.e. lateral):** rebound phenomenon, scanning dysarthria, dysdiadochokinesis, dysmetria, nystagmus

### Symptoms and Signs of Cerebellar Dysfunction

- nystagmus: observe on extra-ocular movement testing (most common is gaze-evoked nystagmus)
- dysarthria (ataxic): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/slurred speech on spontaneous speech (see CN X *Vagus Nerve*, N10)
- ataxia: broad-based, uncoordinated, lurching gait
- dysmetria: irregular placement of voluntary limb or ocular movement
- dysdiadochokinesis: impairment of rapid alternating movements (e.g. pronation – supination task)
- postural instability: truncal ataxia on sitting, titubation (rhythmic rocking of trunk and head), difficulty with tandem and broad-based gait
- intention tremor: typically orthogonal to intended movement, and increases as target is approached
- hypotonia: decreased resistance to passive muscular extension (occurs shortly after injury to lateral cerebellum)
- pendular patellar reflex: knee reflex causes pendular motion of leg (occurs after injury to cerebellar hemispheres)
- rebound phenomenon: overcorrection after displacement of a limb
- ocular apraxia: gaze dysmetria



### Differentiating Ataxia

	Vestibular	Cerebellar	Sensory
Nystagmus/Vertigo	+	±	–
Dysarthria	=	±	–
Limb ataxia	–	+	+
			(esp. legs)
Stance	Worse with eyes closed	Poor with eyes open or closed	+ve Romberg
Vibration/Proprioception	Normal	Normal	Impaired (esp. distal)
Ankle reflexes	Normal	Normal	Decreased/absent

## Wernicke-Korsakoff Syndrome

- see [Psychiatry](#), PS23
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy



## Cerebellar Ataxias



### Congenital Ataxias

- early onset nonprogressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

### Hereditary Ataxias

- **autosomal recessive:** includes Friedrich's ataxia, ataxia telangiectasia, vitamin E deficiency
  - Friedrich's ataxia: prevalence 2/100,000; onset between 8 and 15 yr
    - ♦ signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration, dysarthria
    - ♦ death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- **autosomal dominant:** most commonly spinocerebellar ataxias (30 types, most due to CAG repeats)
  - signs: ataxia and dysarthria;  $\pm$  myoclonus, chorea, polyneuropathy, pyramidal or extrapyramidal features, hyporeflexia, seizures, dementia

### Acquired Ataxias

- **neurodegeneration** (e.g. multiple system atrophy)
- **systemic:** alcohol, celiac sprue, hypothyroidism, Wilson's, thiamine deficiency
- **toxins:** carbon monoxide, heavy metals, lithium, anticonvulsants, solvents
- **vascular:** infarct, bleed, basilar migraine
- **autoimmune:** MS, Miller-Fischer (GBS)

## Vertigo

- see [Otolaryngology](#), OT12



## Gait Disturbances



### Approach to Gait Disturbances

1. **Characterization of the gait disturbance**
  - posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, elaborate/inconsistent movements, standing from sitting
2. **Identification of accompanying neurologic signs**
  - full neurological exam required (diagnosis often can be made by P/E alone)
3. **Identify red flags**
  - sudden onset, cerebellar ataxia, paresis (hemi, para or quadra), bowel/bladder incontinence
4. **Work up**
  - based on etiology – requires blood work, neuroimaging and urgent neurologist referral



#### Central Motor Systems

3 components to the control of gait

- Pyramidal: main outflow from cortex to spinal cord
- Extrapyramidal: basal ganglia inhibits excess movements
- Cerebellum: affects coordination of gait

Table 17. Types of Gait Disturbance

Location	Description	Disorder
Visual loss	Broad based gait with tentative steps	Cataract surgery without lense replacement
Proprioceptive loss	Sensory ataxia: wide-based with high stepping posture and positive Romberg	Demyelinating neuropathies, paraneoplastic syndrome, tabes dorsalis, MS, compressive myelopathy, B <sub>12</sub> deficiency
Peripheral vestibular lesion 1. Acute 2. Bilateral	1. Vestibular ataxia 2. Disequilibrium	1. Tumour, trauma, infectious, Ménière's disease 2. Ototoxic drugs
Peripheral nerve disorder: 1. Foot drop 2. Lumbosacral radiculopathy	Steppage gait	Acquired/hereditary peripheral neuropathy, compressive peroneal neuropathy, L4-5 radiculopathy
Myopathies	Waddling gait: broad based, short stepped gait with pronounced lumbar lordosis, rotation of pelvis	Progressive muscular dystrophy

**Table 17. Types of Gait Disturbance** (continued)

Location	Description	Disorder
<b>Pyramidal/Corticospinal tract lesion</b> 1. Unilateral 2. Bilateral	Spastic gait: spastic foot drop, circumduction, scissoring of legs or toe walking with bilateral circumduction	Unilateral: stroke (ischemic/hemorrhagic) Bilateral: cervical spondylosis, cerebral palsy, spinal cord tumour, combined spinal cord degeneration, MS, motor neuron disease
<b>Basal Ganglia</b>	1. Parkinsonian gait: small paces, stooped posture, reduced arm swing 2. Choreic/hemiballistic/dystonic gait	Infarct, Huntington's, Sydenham's chorea, Wilson's disease, lupus, neuroleptic medications, polycythemia vera, genetic dystonia
<b>Cerebellar Disorder</b>	Cerebellar ataxic gait: wide-based without high stepping; veers to side of lesion Alcoholic gait	Primary and secondary neoplasm, toxins (alcohol), vit. E deficiency, hypothyroid, hypoxia, hypoglycemia, paraneoplastic syndrome

## Motor Neuron Disease

### Amyotrophic Lateral Sclerosis (ALS) (aka Lou Gehrig's Disease)

#### Definition

- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal

#### Etiology

- idiopathic (most), genetic (5-10% familial, especially SOD1 mutation, other: C9orf72, TARDBP)

#### Pathology

- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

#### Epidemiology

- 5/100,000; incidence increases with age

#### Signs and Symptoms

- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms
- bulbar findings: dysarthria (flaccid or spastic), dysphagia, tongue atrophy and fasciculations, facial weakness and atrophy
- pseudobulbar affect, frontotemporal dementia (up to 10%)
- sparing of sensation, ocular muscles and, sphincters

#### Investigations

- EMG: chronic denervation and reinnervation, fasciculations
- NCS : to rule out peripheral neuropathy (i.e. multifocal motor neuropathy with conduction block)
- CT/MRI: to rule out cord disease/compression

#### Management

- riluzole (modestly slows disease progression)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine, regular exercise and physical therapy
  - sialorrhea: TCA (i.e. amitriptyline), sublingual atropine drops, parotid/submandibular botox (rare)
  - pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
  - non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (i.e. PEG tube), rehabilitation (PT, OT, SLP), psychosocial support

#### Prognosis

- median survival 3 yr; death due to respiratory failure



**Red Flags Inconsistent with ALS**  
Sensory sx, predominant pain, bowel or bladder incontinence, cognitive impairment, ocular muscle weakness.



The only interventions that have been shown to extend survival in ALS are riluzole and use of BiPAP.



**Denervation on EMG**  
Fibrillations, positive sharp waves, complex repetitive discharges; reinnervation – increased amplitude and duration of motor units.

## Other Motor Neuron Diseases

- degenerative**
  - progressive muscular atrophy (progressive bulbar palsy):** only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centres
  - primary lateral sclerosis (progressive pseudobulbar palsy):** UMN symptoms, later onset, not fatal with variable disability; 5-10% of patients in ALS centres
  - spinal muscular atrophy:** pediatric disease with symmetric LMN symptoms
- infectious**
  - post-polio syndrome:** residual asymmetric muscle weakness, atrophy
- acquired**
  - multifocal motor neuropathy:** conduction block on NCS, asymmetric LMN symptoms, ± anti-GM1 Ab, treatable with IVIg

# Peripheral Neuropathies



## Diagnostic Approach to Peripheral Neuropathies

1. Differentiate: motor vs. sensory vs. autonomic vs. mixed
2. Pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; cranial nerve involvement
3. Temporal pattern: acute vs. chronic; relapsing remitting vs. constant vs. progressive
4. History: PMH, detailed FHx, exposures (e.g. insects, toxins, sex, travel), systemic symptoms
5. Detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status

## Classification

- **monoradiculopathy**: dermatomal deficit due to single nerve root lesion
  - due to disc herniation or root compression causing radicular pain
  - little tactile anaesthesia, as dermatomes overlap
- **polyradiculopathy**: multiple dermatome deficits due to multiple nerve root lesions
  - one type is cauda equina syndrome (lumbosacral roots)
- **plexopathy**: deficit matching distribution of a nerve plexus
  - **brachial plexopathy**
    - ♦ upper (C5-C7): LMN sx of shoulder and upper arm muscles (Erb's palsy)
    - ♦ lower (C8-T1): LMN sx and sensory sx of forearm and hand (Klumpke's palsy)
    - ♦ DDX: trauma, idiopathic neuritis, tumour infiltration, radiation, thoracic outlet syndrome (i.e. cervical rib)
  - **lumbosacral plexopathy** (rare, especially unilateral)
    - ♦ DDX: idiopathic neuritis, infarction (i.e. diabetes), compression
- **mononeuropathy**: single nerve deficit
  - **carpal tunnel syndrome** (most common): compression of median nerve at wrist
    - ♦ symptoms: wrist pain, paresthesia first 3 and ½ digits, ± radiation to elbow, worse at night
    - ♦ signs: Tinel's sign, Phalen's test, thenar muscle wasting, sensory deficit
    - ♦ EMG and NCS: slowing at wrist (both motor and sensory)
  - **Bell's palsy** (most common cranial neuropathy): see [Otolaryngology](#), OT22
  - other less common mononeuropathies due to entrapment/compression: ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)
- **mononeuropathy multiplex**: deficit affecting multiple discrete nerves (asymmetric)
  - must rule out vasculitis or collagen vascular disease
- **polyneuropathy**: symmetrical distal stocking-glove pattern
  - symmetrical distal sensorimotor deficit affecting longest fibres first (stocking-glove distribution), hypotonia; progression of dysesthesia early and weakness later
  - etiology: DM (most common), renal disease, substances, toxins, genetics, SLE, HIV, leprosy, alcohol, B<sub>12</sub> deficiency, uremia
  - **chronic inflammatory demyelinating polyneuropathy (CIDP)**
    - ♦ chronic relapsing sensorimotor polyneuropathy with increase protein in CSF and demyelination (shown on EMG/NCS)
    - ♦ course is fluctuating, in contrast with the acute onset of GBS
    - ♦ treatment: first-line is prednisone; alternatives are plasmapheresis, IVIg, and azathioprine



**Tinel's Sign:** tap lightly over the median nerve at the wrist. The patient's symptoms of carpal tunnel will be elicited in a positive test.



**Phalen's Test:** hold both wrists in forced flexion (with the dorsal surfaces of the hands pressed against each other) for 30-60 s. Test is positive if symptoms of carpal tunnel are elicited.



### Diabetic Neuropathies

- Peripheral neuropathy: pain or loss of sensation in a glove and stocking distribution (hands and feet affected before arms and legs)
- Autonomic: anhidrosis, orthostatic hypotension, impotence, gastroparesis, bowel and bladder dysfunction
- Mononeuropathy multiplex: nerve infarct or compression
- Cranial neuropathy: CN III (pupil sparing) > IV > VI
- Lumbosacral plexopathy



**DDx of Demyelinating Neuropathy**  
GBS, CIDP, paraproteinemia, diphtheria, amiodarone, Charcot-Marie-Tooth, storage diseases, pressure palsy predisposition, paraneoplastic.



Axonal neuropathies have decreased amplitude on NCS; demyelinating neuropathies have decreased velocity on NCS.



Otolotoxic drugs (e.g. aminoglycosides) should not be given to diabetics. Sensory neuropathy of the feet prevent them from adequately compensating for loss of vestibular function.



### Evaluation of Distal Symmetric Polyneuropathy: Role of Laboratory and Genetic Testing

*Neurology* 2009;72:185-192  
**Screening lab tests:** Blood glucose, serum B12 with metabolites, serum protein immunofixation electrophoresis.  
**Genetic testing:** Indicated for cryptogenic polyneuropathy exhibiting classic hereditary neuropathy phenotype. Screen for CMT1A duplication/deletion and Cx32 mutations.

**Table 18. Differential Diagnosis of Symmetric Polyneuropathy\***

	Etiology	Mechanism	Course	Modalities	Investigations
<b>Vascular</b>	PAN	Ischemic	Chronic	S/M	see <a href="#">Rheumatology</a> , RH19
	SLE	Ischemic	Chronic	S/M	see <a href="#">Rheumatology</a> , RH11
	RA	Ischemic	Chronic	S/M	see <a href="#">Rheumatology</a> , RH8
<b>Infectious</b>	HIV	Axonal/demyelination	Chronic	S/A	HIV serology
	Leprosy	Infiltrative	Chronic	S/A	Leprosy serology Nerve biopsy
	Lyme	Axonal/demyelination	Chronic	M	Lyme serology
<b>Immune</b>	GBS	Demyelination	Acute	M	LP (↑ protein; no ↑ cells)
	CIDP	Demyelination	Chronic	S/M	LP (↑ protein)
<b>Hereditary</b>	HMSN	Axonal/demyelination	Chronic	S/M	Genetic testing
<b>Neoplastic</b>	Paraneoplastic	Axonal/demyelination	Chronic	S/M	Paraneoplastic antibodies
	Myeloma	Axonal/demyelination	Chronic	S/M	SPEP Skeletal bone survey
	Lymphoma	Axonal	Chronic	M	SPEP Bone marrow biopsy
	Monoclonal gammopathy	Demyelination	Chronic	S/M	SPEP Bone marrow biopsy
<b>Toxin</b>	EtOH	Axonal	Sub-acute	S/M	GGT, MCV
	Heavy metals	Axonal	Sub-acute	S/M	Urine heavy metals
	Medications	Axonal	Sub-acute	S/M	Drug levels



**Table 18. Differential Diagnosis of Symmetric Polyneuropathy\*** (continued)

	Etiology	Mechanism	Course	Modalities	Investigations
<b>Metabolic</b>	Diabetes	Ischemic/axonal	Chronic	S/A	Fasting glucose, HbA1c, 2 h OGTT
	Hypothyroidism	Axonal	Chronic	S/M	TSH, T <sub>3</sub> , T <sub>4</sub>
	Renal failure	Axonal	Chronic	S/A	Electrolytes, Cr, BUN
<b>Nutritional</b>	B <sub>12</sub> deficiency	Axonal	Sub-acute	S/M	Vitamin B <sub>12</sub>
<b>Other</b>	Porphyria	Axonal	Sub-acute	M	Urine porphyrins
	Amyloid	Axonal	Sub-acute	S	Nerve biopsy

\*Abbreviations: CIDP – chronic inflammatory demyelinating polyradiculoneuropathy; GGT – gamma-glutamyl transferase; HMSN – hereditary motor sensory neuropathy; OGTT – oral glucose tolerance test; PAN – polyarteritis nodosa; RA – rheumatoid arthritis; SLE – systemic lupus erythematosus; SPEP – serum protein electrophoresis; S – sensory; M – motor; A – autonomic

### Guillain-Barré Syndrome (GBS)

- definition:** acute rapidly evolving polyneuropathy that often starts in the distal lower limbs and ascends
- etiology**
  - autoimmune attack and damage to peripheral nerve myelin
  - sometimes preceded by viral/bacterial infections
- signs and symptoms**
  - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
  - motor: weakness starting distally in legs, areflexia
  - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- investigations**
  - CSF: albuminocytological dissociation (high protein, normal WBC)
  - EMG/NCS: conduction block, differential or focal (motor>sensory) slowing, decreased F-wave, sural sparing
- subtypes**
  - acute inflammatory demyelinating polyneuropathy (AIDP)
  - acute motor-sensory axonal neuropathy (AMSAN)
  - acute motor axonal neuropathy (AMAN)
- treatment**
  - IVIg or plasmapheresis, ± pain management, monitor vitals and vital capacity
- prognosis**
  - peak of symptoms at 2-3 wk, resolution at 4-6 wk
  - 5% mortality (higher if require ICU); up to 15% have permanent deficits



GBS is a neurological emergency due to risk of imminent respiratory failure.



The most common antecedent infection in GBS is *Campylobacter jejuni*.



#### Miller-Fischer Variant of GBS – Triad

- Ophthalmoplegia
- Ataxia
- Areflexia



IVIg and plasmapheresis lead to more rapid improvement, less intensive care and less ventilation, but do not change mortality or relapse rate.



## Neuromuscular Junction Diseases

### Clinical Approach to Disorders of the Neuromuscular Junction

**Table 19. Common Disorders of the Neuromuscular Junction**

	Myasthenia Gravis	Lambert-Eaton	Botulism
Ocular/bulbar paresis	+	–	++ (early)
Limb weakness	+	+	+
Fatiguability	+	+	+
Post-exercise enhancement	–	+	+
Reflexes	N	↓	↓
Anticholinergic sx	–	+	++
Sensory sx	–	–	–
Associated conditions	Thymoma	Small cell carcinoma	GI S&S
Repetitive EMG stimulation	Decremental response	Incremental response	↑ (rapid stimulation) ↓ (slow stimulation)



Diseases of the neuromuscular junction typically feature prominent fatiguability. Fatiguability can be tested by holding the arms out, or by holding the gaze in the upward position (especially in MG). Muscle weakness due to fatiguability will improve with rest or ice.

### Myasthenia Gravis (MG)

#### Etiology and Pathophysiology

- progressive autoimmune disorder due to anti-AChR antibodies, resulting in early saturation at the NMJ and inadequate muscle activation with increasing nerve stimulation
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia

### Epidemiology

- bimodal age of onset – 20s (mostly women) and 60s (mostly men)

### Signs and Symptoms

- see Table 19
- fatiguable, symmetric or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
- ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
- symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
- respiratory muscle weakness may lead to respiratory failure

### Investigations

- edrophonium (Tensilon®) test
  - assess for improvement over 2 min following edrophonium injection
- EMG
  - repetitive stimulation → decremental response
  - single fibre electromyography shows increased jitter (80-100% sensitivity)
- spirometry – forced vital capacity may be used to monitor adequacy of respiratory effort over time
- anti-acetylcholine receptor antibody assay (70-80% sensitivity)
- MUSK antibody may be used if seronegative for AChR antibody
- CT/MRI to screen for thymoma/thymic hyperplasia

### Treatment

- thymectomy
  - 85% of patients show improvement or remission
- symptomatic relief
  - acetylcholinesterase inhibitors (e.g. pyridostigmine)
  - does not affect primary pathologic process so rarely results in control of disease when used alone
- immunosuppression
  - steroids are mainstay of treatment (70-80% remission rate)
  - azathioprine, cyclophosphamide and mycophenolate as adjuncts or as steroid sparing therapy
- short-term immunomodulation (for crises)
  - IVIg and plasmapheresis

### Prognosis

- 30% eventual spontaneous remission
- with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

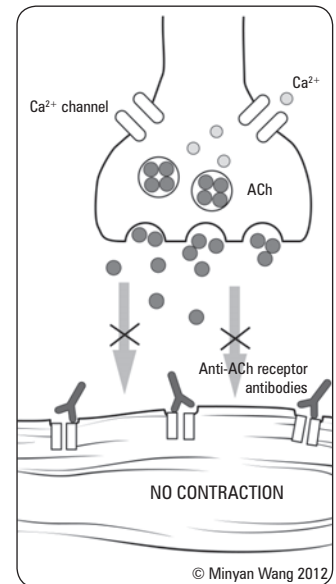


Figure 22. Myasthenia gravis



Tensilon® is a drug that inhibits acetylcholinesterase. It improves muscle function immediately in myasthenia gravis, but not in a cholinergic crisis. This test is infrequently used. When performed, a crash cart should be nearby as respiratory difficulty and/or bradycardia may occur.



**LEMS**  
On exam there is initial post-exercise enhancement, but with prolonged effort muscles will fatigue.

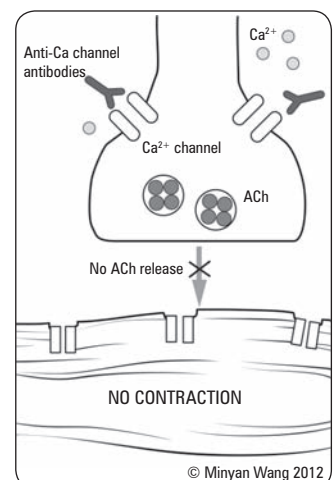


Figure 23. Lambert-Eaton myasthenic syndrome (LEMS)

## Lambert-Eaton Myasthenic Syndrome (LEMS)

### Etiology and Pathophysiology

- autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased ACh release at the NMJ
- 50-66% are associated with small cell carcinoma of the lung

### Signs and Symptoms

- see Table 19
- weakness of skeletal muscles without sensory or coordination abnormalities
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and ocular muscles affected in 25% (vs. 90% in MG)
- prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

### Investigations

- edrophonium test (see *Myasthenia Gravis*, N32) → no response
- EMG
  - rapid (>10 Hz) repetitive stimulation → incremental response
  - post-exercise facilitation → an incremental response with exercise
- screen for malignancy, especially small cell lung cancer

### Treatment

- tumour removal
- acetylcholine modulation
  - increased acetylcholine release (3,4-diaminopyridine)
  - decreased acetylcholine degradation (pyridostigmine)
- immunomodulation
  - steroids, plasmapheresis, IVIg



## Botulism

### Etiology and Pathophysiology

- caused by a toxin produced by spores of *Clostridium botulinum* bacteria, which is found in soil and water throughout the world. Bacteria can enter the body through wounds or by ingesting improperly preserved foods
- infantile botulism is the most common form, and is usually from ingestion of honey or corn syrup

### Signs and Symptoms

- occur 6-48 h after ingestion
- difficulty with convergence, ptosis, paralysis of extraocular muscles
- dilated, poorly reactive pupils
- other autonomic dysfunction: jaw weakness, dysarthria, dysphagia
- spreads to trunk and limbs
  - abdominal cramps with nausea and vomiting
  - symmetric weakness with paralysis and absent/decreased deep tendon reflexes
  - anticholinergic symptoms: dry mouth, constipation, urinary retention
- rarely respiratory distress, potentially advancing to respiratory failure

### Investigations

- blood test for toxin
- stool culture

### Treatment

- botulinum anti-toxin – good prognosis with prompt treatment
- supportive therapy as required

## Myopathies

### Clinical Approach to Muscle Diseases

Table 20. Myopathies

	Etiology	Key Clinical Features	Key Investigations
Inflammatory	Polymyositis	Myalgias Pharyngeal involvement	↑ CK Biopsy: endomysial infiltrates; necrosis
	Dermatomyositis	Myalgias Characteristic rashes Can be paraneoplastic	↑ CK Biopsy: perifascicular atrophy
	Sarcoidosis	See <a href="#">Respirology</a> , R13	ACE level Biopsy: granulomas
	Inclusion body myositis	Weak quadriceps and deep finger flexors	↑ CK Biopsy: inclusion bodies
Endocrine	Thyroid (↑ or ↓) Cushing's syndrome Parathyroid (↑ or ↓)	See <a href="#">Endocrinology</a> , E20, E33	TSH, serum cortisol, calcium panel
Toxic	Medication	Medication or toxin history	Toxicology screen
	Critical illness myopathy	ICU patient Hx steroids and nondepolarizing paralyzing agents Failure to wean from ventilation	Biopsy: selective loss of thick myosin filaments
Infectious	Parasitic, bacterial or viral	Myalgias Inflammatory myopathy	↑ myoglobin
Hereditary dystrophy	Duchenne	Early onset (Duchenne and Becker)	Dystrophin analysis: absent
	Becker	Progressive proximal muscle weakness Calf pseudohypertrophy	Dystrophin analysis: abnormal
	Myotonic dystrophy	Distal myopathy Myotonia Genetic anticipation	Genetic testing
Hereditary metabolic	McArdle's	Exercise-related myalgias, cramping, and myoglobulinuria	↑ lactate ↑ serum/urinary myoglobin post-exercise
Hereditary periodic paralysis	"Channelopathy"	Episodic weakness Normal between attacks	Normal, ↑ or ↓ K <sup>+</sup>



Myopathies are characterized by prominent symmetric proximal weakness and absent sensory changes.



#### Good Questions to Assess Proximal Weakness

- Legs: climbing stairs, stand from sit
- Arms: reach above head, wash hair



#### Common Medications that Cause Myopathy:

steroids, statins, antiretrovirals, thyroxine, fibrates, cyclosporine, ipecac.

**Common Drugs that Cause Myopathy:** ethanol, cocaine, heroin.

**Table 20. Myopathies** (continued)

	Etiology	Key Clinical Features	Key Investigations
<b>Hereditary mitochondrial</b>	MERRF	Myoclonus, generalized seizures, dementia, myopathy	Biopsy: ragged red fibres Increased lactate
	MELAS	Pediatric onset, stroke-like symptoms, episodic vomiting, dementia	
	Kearns Sayre	Progressive ophthalmoplegia, retinal pigment degeneration, cardiac conduction abnormalities	

MERRF = mitochondrial encephalomyopathy with ragged red fibers; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

## Polymyositis/Dermatomyositis

- see [Rheumatology](#), RH15



## Myotonic Dystrophy

### Etiology and Pathophysiology

- unstable trinucleotide (CTG) repeat in DMK gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms
- autosomal dominant

### Epidemiology

- most common adult muscular dystrophy
- prevalence 3-5/100,000

### Signs and Symptoms

- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance
- physical exam
  - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
  - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
  - cardiac: 90% have conduction defects (1° heart block; atrial arrhythmias)
  - respiratory: hypoventilation 2° to muscle weakness
  - ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
  - other: diabetes, infertility, testicular atrophy
- EMG: subclinical myotonia – long runs with declining frequency and amplitude

### Treatment and Prognosis

- no cure, progressive, death usually around 50 yr
- management of myotonia: phenytoin

## Duchenne and Becker Muscular Dystrophy

- see [Pediatrics](#), P44



## Pain Syndromes



## Approach to Pain Syndromes

### Definitions

- **nociceptive pain:** pain arising from normal activation of peripheral nociceptors
- **neuropathic pain:** pain arising from direct injury to neural tissue, bypassing nociceptive pathways
- **spontaneous pain:** unprovoked burning, shooting, or lancinating pain
- **paresthesiae:** spontaneous abnormal nonpainful sensations (e.g. tingling)
- **dysesthesiae:** evoked pain with inappropriate quality or excessive quantity
- **allodynia:** a dysesthetic response to a non-noxious stimulus
- **hyperalgesia:** an exaggerated pain response to a noxious stimulus



- Pinprick sensation mediated by Aδ fibers
- Pain due to tissue damage is mediated by C fibres

### Non-pharmacological Management

- physical (PT, acupuncture, chiropractic manipulation, massage)
- psychoeducational (CBT, family therapy, education, psychotherapy)

### Medical Pain Control

- combination multi-modal therapy is important
- primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches and arthritis), opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympatholytics (phenoxybenzamine),  $\alpha$ 2-adrenergic agonists (clonidine)

### Surgical Pain Control

- peripheral ablation: nerve blocks, facet joint denervation
- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy or dorsal root entry lesion
- DBS or dorsal column stimulation



#### WHO Pain Ladder

- **Mild pain:** Non-opioid (acetaminophen and/or NSAID)  $\pm$  adjuvant
- **Moderate pain:** Opioid for mild to moderate pain (codeine/oxycodone) + non-opioid  $\pm$  adjuvant
- **Severe pain:** Opioid for moderate to severe pain (morphine/hydromorphone) + non-opioid  $\pm$  adjuvant



Axonal regeneration is directed by intact nerve sheaths. If the nerve sheath is damaged, axons grow without direction, become tangled and form a neuroma, which can result in ectopic electrical impulses and neuropathic pain.

## Neuropathic Pain

### Definition

- pain resulting from a disturbance of the central or peripheral nervous system

### Symptoms and Signs

- hyperalgesia/allodynia
- subjectively described as burning, heat/cold, pricking, electric shock, perception of swelling, numbness (i.e. stocking/sock distribution)
- can be spontaneous or stimulus evoked
- distribution may not fall along classical neuro-anatomical lines
- associated issues: sleep difficulty, anxiety/stress/mood alteration

### Causes of Neuropathic Pain

- **sympathetic**
  - complex regional pain syndrome
- **central:** abnormal CNS activity
  - phantom limb, post spinal cord injury, post stroke, MS
- **non-sympathetic:** damage to peripheral nerves
  - **systemic disease:** DM, thyroid disease, renal disease, rheumatoid arthritis
  - **nutritional/toxicity:** alcoholism, pernicious anemia, chemotherapy
  - **infectious:** post-herpetic, HIV
  - **trauma/compression:** nerve entrapment, trigeminal neuralgia, post surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy

### Treatment

- identify/treat underlying cause
- **pharmacotherapy**
  - Stepwise approach (*Canadian Pain Society*, 2007): TCA, anticonvulsant, SNRI, topical lidocaine, long acting opiate (caution), tramadol
  - other: capsaicin cream, intrathecal opioid or clonidine, botulinum toxin injection, nerve block
- **common non-pharmacologic therapies**
  - neuropsychiatry: cognitive behavioural therapy, psychotherapy
  - rehabilitation: physiotherapy
  - complementary and alternative medicine: acupuncture, meditation, massage therapy, traditional Chinese medicine
- **surgical therapies:** dorsal column neurostimulator, DBS (thalamus)

## Tic Douloureux (Trigeminal Neuralgia)

### Clinical Features

- recurrent episodes of sudden onset, excruciating unilateral paroxysmal shooting "electric" pain in trigeminal root territory (V3>V2>>V1)
- may have normal sensory exam
- pain lasts seconds/minutes over days/weeks; may remit for weeks/months
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up

**Etiology**

- **classic TN:** idiopathic
- **secondary TN:** compression by tortuous blood vessel (superior cerebellar artery), cerebellopontine angle tumour (5%), multiple sclerosis (5%)

**Epidemiology**

- F > M; usually middle-aged and elderly

**Diagnosis**

- clinical diagnosis
- investigate for secondary causes, which are more likely if bilateral TN or associated sensory loss
  - MRI to rule out structural lesion, MS or vascular lesion

**Treatment**

- first line: carbamazepine or oxcarbazepine
- second line: baclofen or lamotrigine
- narcotics not generally recommended
- if medical treatment fails: Gasserian ganglion percutaneous technique, gamma knife, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression

## Postherpetic Neuralgia (PHN)

**Clinical Features**

- pain persisting in the region of a cutaneous outbreak of herpes zoster
- constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
- distribution: thoracic, trigeminal, cervical > lumbar > sacral
- associated impaired sleep, decreased appetite, decreased libido

**Etiology and Pathogenesis**

- destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

**Epidemiology**

- incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
- risk factors: older age, greater acute pain, greater rash severity

**Prevention**

- varicella zoster vaccine in childhood reduces incidence of varicella zoster
- herpes zoster vaccine (Zostavax®) reduces incidences of shingles, PHN and other herpetic sequel (currently recommended in Canada for those >60 yr old)

**Treatment**

- medical: TCA (i.e. amitriptyline), anti-convulsants (i.e. pregabalin, gabapentin), analgesia (i.e. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  - early treatment of acute herpes zoster with antivirals (acyclovir; longer-acting famciclovir and valacyclovir more effective)
  - treatment of herpes zoster with corticosteroids DOES NOT decrease PHN
- surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus



**Herpes zoster of trigeminal nerve:** typically involves V1 (ophthalmic division).

**Hutchinson's sign:** tip of nose involvement predicts corneal involvement.

## Painful Diabetic Neuropathy

**Approach**

- determine if pain is neuropathic or vascular
- more likely neuropathic if:
  - feet > calves
  - sharp/tingling pain
  - pain present at rest and improves with walking

**Treatment**

- Level A: pregabalin
- Level B: venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, rarely opioids, capsaicin

## Complex Regional Pain Syndromes (CRPS)

### Clinical Features

- presence of an initiating noxious event (MI, stroke)
- continuing pain, allodynia, or hyperalgesia with pain disproportionate to inciting event
- evidence during the course of symptoms of edema, changes in skin blood flow or abnormal vasomotor activity
- absence of conditions that would otherwise account for degree of pain and dysfunction
- other features can include edema, osteoporosis, hyperhydrosis, hair loss, fascial thickening

### Classification

- **CRPS type I (reflex sympathetic dystrophy):** minor injuries of limb or lesions in remote body areas precede onset of symptoms
- **CRPS type II (causalgia):** injury of peripheral nerves precedes the onset of symptoms

### Investigations

- trial of differential neural blockade may be helpful in diagnosis
- autonomic testing (evidence of sympathetic dysfunction)
- bone scan, plain radiography, MRI

### Prevention

- early mobilization after injury/infarction

### Treatment

- goal of treatment: to facilitate function
- conservative treatment: education, support groups, PT/OT, smoking cessation
- medical: topical capsaicin, TCA, NSAID, tender point injections with corticosteroid/lidocaine, gabapentin/pregabalin/lamotrigine, calcitonin or bisphosphonates, oral corticosteroids
- surgical: paravertebral sympathetic ganglion blockade
- refer to pain management clinic



#### Prescribing of Opioid Analgesics and Related Mortality Before and after the Introduction of Long-Acting Oxycodone

CMAJ 2009;181:891-896

**Study:** Epidemiological study of 3271 opioid related deaths from 1991-2007 that assessed association with introduction of long-acting oxycodone to the Ontario provincial formulary.

**Results:** Opioid related deaths increased significantly in association with introduction of long acting oxycodone.

**Conclusion:** Opioids must be used cautiously given serious potential harm, and careful monitoring is required.



If CT is negative but clinically there is suspicion of SAH or meningitis, perform a lumbar puncture.



#### Headache DDx

##### ER VISIT

**Eye** (acute angle closure glaucoma, sinusitis)

**Recurrent/Chronic** (migraine, tension, cluster, TMJ disease, cervical OA)

**Vascular** (SAH, ICH, temporal arteritis)

**Infectious** (meningitis, encephalitis)

**Systemic** (anemia, anoxia, CO, pre-eclampsia)

**ICP** (mass/abscess, HTN encephalopathy, pseudotumour cerebri)

**Trauma** (concussion, SDH, EDH)

## Headache

- see [Emergency Medicine](#), ER24 and [Family Medicine](#), FM36

### Clinical Approach

- **history**
  - pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g. worse in AM, worse with bending/cough/Valsalva)
  - associated symptoms: visual changes, change in mental status, nausea/vomiting, fever, meningismus, photophobia, phonophobia, TMJ popping/clicking, jaw claudication, neurological sx
  - precipitating/alleviating factors (triggering factors, analgesics), medications (esp. nitrates, CCBs, NSAIDs, anticoagulants), PMH, FHx
  - red flags (possible indications for CT scan/further investigation): new-onset headache (esp. if age <5 or >50), quality worse/different than previous headaches, sudden and severe ('thunderclap'), immunocompromised, fever, focal neurological deficits, trauma
- **physical**
  - vitals (including BP and temp), Kernig's/Brudzinski's, MSK examination of head and neck
  - HEENT: fundi (papilledema, retinal hemorrhages), red eye, temporal artery tenderness, sinus palpation, TMJ
  - full neurologic exam (including LOC, orientation, pupils (symmetry), and focal neurological deficits)
  - **red flags:** papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

### Classification

- **primary**
  - tension, migraine, cluster, exertional, cervical OA, TMJ syndrome
- **secondary**
  - SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN or pseudotumour cerebri), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-eclampsia, post lumbar puncture, drugs/toxins (e.g. nitroglycerin use and analgesia withdrawal); all can be associated with serious morbidity or mortality

Table 21. Headaches – Selected Primary Types

	Tension-Type	Migraine	Cluster
<b>Prevalence</b>	70%	12%	<1%
<b>Age of Onset</b>	15-40	10-30	20-40
<b>Sex Bias</b>	F > M	F > M	M > F
<b>Family History</b>	None	+++	+
<b>Location</b>	Bilateral frontal Nuchal-occipital	Unilateral>bilateral Fronto-temporal	Retroorbital
<b>Duration</b>	Minutes – days	Hours – days	10 min-2 h
<b>Onset/Course</b>	Gradual; worse in PM	Gradual; worse in PM	Daily attacks for weeks to months; more common early AM or late PM
<b>Quality</b>	Band-like; constant	Throbbing	Constant, aching, stabbing
<b>Severity</b>	Mild-moderate	Moderate-severe	Severe (wakes from sleep)
<b>Triggers/Provoking</b>	Depression Anxiety Noise Hunger Sleep deprivation	Noise/light Caffeine/alcohol Hunger Stress Sleep deprivation	Light EtOH
<b>Palliating</b>	Rest	Rest	Walking around
<b>Associated Sx</b>	No vomiting No photophobia	Nausea/vomiting Photo/phonophobia Aura	Red watery eye Nasal congestion or rhinorrhea Unilateral Horner's
<b>Management</b>	Non-pharmacological • Psychological counseling • Physical modalities (e.g. heat, massage) Pharmacological • Simple analgesics • Tricyclic antidepressants	Acute Rx • ASA • NSAIDs • Triptans • Ergotamine Prophylaxis 1. TCA 2. Anticonvulsants 3. Propranolol	Acute Rx • O <sub>2</sub> • Sumatriptan (nasal or injection) Prophylaxis • Verapamil • Lithium • Methysergide • Prednisolone

Table 22. Prophylactic Management of Migraine Headaches

Class	Drug	Evidence	Contraindications	Side Effects
<b>Beta-blockers</b>	Propranolol	A	Asthma, DM (mask hypoglycemia)	Fatigue
	Timolol	A		Depression
	Metoprolol	B	CHF	Light-headedness
<b>TCA</b>	Amitriptyline	A	Heart disease, glaucoma	Sedation
	Nortriptyline	C	*Avoid in elderly	Dry mouth Weight gain Light-headedness
<b>CCB's</b>	Flunarizine	A	Depression, obesity	Weight gain, depression, PD (rare)
	Verapamil	B	Heart disease	Weight gain (10-20 lb), constipation
<b>AED</b>	Valproate	A	Liver, renal, pancreatic diseases	Weight gain, tremor, alopecia, teratogenic: N.T. defect
	Topiramate + folic acid supplement	A	Renal	Paresthesia, weight LOSS, cognitive: memory loss, difficulty concentrating, renal stone (rare)

Table 23. Headaches – Selected Serious but Rare Secondary Types

	Meningeal Irritation	Increased ICP	Temporal Arteritis
<b>Age of Onset</b>	Any age	Any age	> 60
<b>Location</b>	Generalized	Any location	Temporal
<b>Onset/Course</b>	Meningitis: hours-days SAH: thunderclap onset	Gradual; worse in AM	Variable
<b>Severity</b>	Severe	Severe	Variable; can be severe
<b>Provoking</b>	Head movement	Lying down Valsalva Head low Exertion	Jaw claudication
<b>Associated Sx</b>	Neck stiffness Photophobia Focal deficits (e.g. CN palsies)	Nausea/vomiting Focal neuro symptoms Decreased level of consciousness	Polymyalgia rheumatica Visual loss



#### The Rational Clinical Examination: Does this Patient with Headache have a Migraine or Need Neuroimaging?

JAMA 2006;296:1274-1283

Does this patient with headache have a migraine? The most useful panel of questions for diagnosing migraine is summarized by the POUNDING mnemonic:

- P** – Pulsatile quality
- O** – duration of 4-72 h
- U** – Unilateral location
- N** – Nausea or vomiting
- D** – Disabling intensity

The LR for definite or possible migraine diagnosis varies with the number of features present: with ≥4, 3 and ≥2 features, the LRs are 24 (1.5-388), 3.5 (1.3-9.2) and 0.41 (0.32-0.52) respectively.

#### Does this patient with headache need neuroimaging?

In patients with new or changed headache the prevalence of significant intracranial pathology is 32% (24-42%), and in those presenting with thunderclap headache the prevalence is 43% (20-68%).

Several individual clinical features were found to be predictive of significant intracranial pathology:

Symptom	OR
Cluster-type headache	10.7 (2.2-52)
Abnormal neurological exam	5.3 (2.4-12)
Undefined-type headache (non-tension/migraine/cluster-type)	3.8 (2.0-7.1)
Headache with aura	3.2 (1.6-6.6)
Aggravated by exertion/Valsalva	2.3 (1.4-3.8)
Headache with vomiting	1.8 (1.2-2.6)



#### Acute and Preventive Pharmacologic Treatment of Cluster Headache

Neurology 2010;75:463-473

**Study:** Meta-analysis of prospective, double-blind, RCTs of pharmacologic agents for prevention or treatment of CH.

**Results:** 27 trials were included. Sumatriptan 6 mg SC, zolmitriptan nasal spray 5-10 mg, and 100% oxygen 6-12 L/min received Level A recommendation for acute treatment. For prevention, Level B recommendations were given for intranasal civamide 100 ug daily and suboccipital steroid injections.

**Conclusion:** Sumatriptan, zolmitriptan, and mid flow oxygen are effective acute treatments for CH.



#### Anticonvulsants in Migraine Prophylaxis

Cochrane DB Syst Rev 2009;3:CD003226

**Study:** Meta-analysis of prospective, controlled trials of anticonvulsant drugs in migraine headache prophylaxis.

**Results:** Twenty-three studies (n=2927) were included. Anticonvulsants reduce migraine frequency by 1.3 attacks per 28 d compared to placebo and double the number of patients for whom migraine frequency is reduced by 50% (RR=2.25, NNT=3.9). Valproate and topiramate are better than placebo, while clonazepam, acetazolamide, lamotrigine and vigabatrin are not. Clinically important adverse events were associated with valproate and topiramate with NNH 7.0 to 18.8 and 2.4 to 31.2 respectively.

**Conclusion:** Anti-convulsants are effective in reducing migraine frequency and reasonably well-tolerated. Valproate and topiramate are the two most studied but further studies of head-to-head comparisons between agents is needed.



**Table 23. Headaches – Selected Serious but Rare Secondary Types** (continued)

	Meningeal Irritation	Increased ICP	Temporal Arteritis
<b>Physical Signs</b>	Kernig's sign Brudzinski's sign Meningismus	Focal neuro symptoms Papilledema	Temporal artery changes: • Firm, nodular, incompressible • Tender
<b>Management</b>	CT/MRI with gadolinium/ LP, antibiotics for bacterial meningitis	CT/MRI and treatment to reduce pressure See <a href="#">Neurosurgery</a> , NS6	Prednisone See <a href="#">Rheumatology</a> , RH20
<b>Etiology</b>	Meningitis, SAH	Tumour, ITH, malignant hypertension	Vasculitis (GCA)

ITH – idiopathic intracranial hypertension



The oral contraceptive pill is contraindicated with complicated migraine due to risk of stroke.



Migraine auras can mimic other causes of transient neurological deficits (e.g. TIAs and seizures).



**"Menstrual Migraine" Subtype**  
Migraine headache that is associated with the onset of menstruation – usually 2 d before to 3 d after the onset of menstrual bleeding.



If patient presents to ED with severe migraine and nausea/vomiting – consider treating with IV anti-emetics (chlorpromazine, prochlorperazine).



#### Pharmacological Treatments for Acute Migraine

Pain 2002;97:247-257

**Study:** Meta-analysis of 54 double-blind, placebo-controlled RCTs of pharmacologic treatment of acute migraine of moderate to severe intensity (21,022 patients in total).

**Data extraction:** Number of patients, dosing regimens, details of study design, and timing or type of rescue medication. Outcomes include headache relief at 1 and 2 h, freedom from pain at 2 h, sustained relief for 24 h, and adverse effects within 24 h.

**Main Results:** Data were available for 9 oral medications, 2 intranasal medications, and subcutaneous sumatriptan. For h/a relief at 2 h, all interventions were effective except Cafergot®, with NNTs ranging from 2.0 for sumatriptan 6 mg SC to 5.4 for naratriptan 2.5 mg. The lowest NNT for oral medication was 2.6 for eletriptan 80 mg. For patients pain free at 2 h, the lowest NNT was 2.1 for sumatriptan 6 mg SC, with the lowest NNT for oral medication being 3.1 for rizatriptan 10 mg. For sustained relief over 24 h NNT ranged from 2.8 for eletriptan 80 mg to 8.3 for rizatriptan 5 mg. Side effects could not be analyzed systematically. There were no drug-to-drug comparisons.

**Conclusion:** Overall, most treatments were effective. Subcutaneous sumatriptan and oral triptans were most effective.



A prophylactic agent is recommended only if migraine attacks are severe enough to cause impairment of a patient's quality of life or if a patient has >3 migraines/month that have not responded adequately to treatment.

Neurology 2000;55:754-763

## Migraine Headaches

### Definition (common migraine)

- ≥5 attacks fulfilling each of the following criteria
  - 4-72 h duration
  - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  - 1 of the following: nausea/vomiting, photophobia/phonophobia/osmophobia

### Epidemiology

- 18% females, 6% males; frequency decreases with age (especially at menopause)

### Etiology and Pathophysiology

- theories of migraine etiology:
  - depolarizing wave of "cortical spreading depression" across the cerebral cortex that may cause an aura (e.g. visual symptoms due to wave through occipital cortex) and also activate trigeminal nerve afferent fibres
  - possible association with vasoconstriction/dilation
- significant genetic contribution
- **triggers:** stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrites (e.g. processed meats)

### Signs and Symptoms

- stages of uncomplicated migraine
  - i. prodrome (hours to days before headache onset)
  - ii. aura
  - iii. headache (see Table 21 for description of typical headache)
  - iv. postdrome
- aura
  - fully reversible symptom of focal cerebral dysfunction lasting <60 min
  - examples: visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots), unilateral paresthesia and numbness or weakness, aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
- classification of migraines
  - common migraine: no aura
  - classic migraine: with aura (headache follows reversible aura within 60 min)
  - complicated migraine: with severe/persistent sensorimotor deficits
    - ♦ examples:
      - basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness)
      - hemiplegic/hemisensory migraine
      - ophthalmoplegic migraine
  - acephalgic migraine (i.e. migraine equivalent): aura without headache

### Management

- avoid triggers
- mild to moderate migraine
  - 1st line: NSAIDs (ibuprofen, naproxen)
- moderate to severe migraine
  - triptans (most effective), ergots (dihydroergotamine, DHE)
- migraine prophylaxis: anticonvulsants (divalproex, topiramate, gabapentin), TCA (amitriptyline, nortriptyline), propranolol, calcium channel blocker (verapamil)

# Sleep Disorders

## Overview of Sleep

### Definition

- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many elderly have reduced sleep as a consequence of underlying sleep disorders

### Sleep Architecture

- **polysomnogram (PSG) measures:** EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG

**Table 24. Sleep Stage Characteristics**

	EEG	EOG	Muscle Tone	Other Characteristics
Waking State	Low voltage high frequency, dominant $\alpha$ rhythm (8-13 Hz)	Rapid, blinking	High	
Stage N1 (~5%)	<50% $\alpha$ activity replaced with $\theta$ (4-7 Hz). Vertex waves	Slow, roving eye movements	High, but gradually dropping	Marker for very light quality sleep or sleep disruption
Stage N2 (~50%)	K complexes high voltage negative and positive discharges with spindles (11-16 Hz)	Still	High	
Stage N3 (previously 3 and 4)/Slow Wave/Delta Sleep (~20%)	Slow wave activity – high voltage (>75 $\mu$ V), low frequency (<2 Hz)	Still	Low	Homeostatic sleep Reduced BP, HR, cardiac output, RR Growth hormone release
Rapid Eye Movement (REM) Sleep (~25%)	Mixed frequency, low voltage, sawtooth waves	Rapid eye movements	Very low	Irregular respiration Arrhythmias, heart rate variation Classical dreaming state



### Element of Sleep History

- Initiation of sleep
  - Events prior to bed
  - Lights
  - Latency (estimated)
  - Restless legs
  - Hallucinations
- Maintaining sleep
  - Number of wakeups/night
  - Sleep walking/talking
  - Snoring/gasping
  - Dreams/nightmares
- Consequences of sleep
  - Restorative
  - Morning headache
  - Falling asleep in inappropriate setting



### Drug Effects on Wakefulness and Sleep

- Antihistamines associated with increased sleepiness
- Stimulants increase arousal
- Caffeine (an adenosine antagonist) increase wakefulness
- Benzodiazepines reduce slow wave sleep
- Antidepressants (TCA/MAO-I/SSRI) reduce REM, prolong REM latency
- Alcohol may hasten sleep onset but associated with increased arousals



Avoid sleep medications (esp. in elderly patients) due to increased risk of falls, pseudodepression, memory loss.

## Disturbances of Alertness and Sleep

### Coma

- see [Neurosurgery](#), NS34

### Insomnia

- **definition/criteria:**
  - difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep
- **types:**
  - sleep state misperception, psychophysiologic insomnia (learned sleep-preventing associations – i.e. clock watching), fatal familial insomnia (rare prion protein mutation causing autonomic dysfunction), idiopathic (lifelong difficulty)
  - **secondary causes:**
    - ♦ psychiatric disorders (80% of psychiatric patients): anxiety and depression (see [Psychiatry](#), PS10, PS13)
    - ♦ neurologic disorders: neurodegenerative disease, epilepsy, neuromuscular disorders, many others
    - ♦ sleep disorders: restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
    - ♦ medical conditions: pregnancy, cardiorespiratory (COPD/HF), GERD, pain (arthritis, fibromyalgia, cancer)
    - ♦ drugs/toxins: caffeine, alcohol, stimulants, antidepressants, glucocorticoids, sedative withdrawal
- **treatment:**
  - sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, cognitive behavioral therapy

**Sleep Apnea**

- **definition**
  - disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence
- **epidemiology:**
  - >2-4% of the population
  - increasing obesity
  - significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)
- **types:**
  - obstructive sleep apnea: see [Respirology](#), R31
  - central sleep apnea: no effort to breathe over 10 s
  - mixed apnea: starts as central, but eventually becomes obstructive
- **etiology of central apnea:** heart failure, opiates, brainstem pathology, myotonic dystrophy
- **diagnosis:** apnea hypopnea index (AHI) or respiratory disturbance index (RDI) should be <5 in the normal or pathologic state
- **treatment:** conservative measures, dental devices, CPAP (common), surgery (rare), ensure driving safety

**Restless Leg Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD)**

- **definition:**
  - urge to move with accompanied uncomfortable sensations that begin or worsen with rest, are partially or totally relieved with movement, and are worse in evening/night
  - RLS refers to sensation
  - PLMD refers to the manifestation
- **epidemiology:** 10% North Americans, 90% of RLS have PLMD, 50% of PLMD have RLS
- **etiology:** central (spasticity), or peripheral nervous system (radiculopathy, neuropathy), pregnancy, iron deficiency, alcohol use
- **treatment:**
  - underlying contributors (iron and B<sub>12</sub> supplementation), dopaminergic agonists (first line), clonazepam (causes tachyphylaxis), opioids (only exceptional circumstances)
  - NOT recommended: Sinemet®, causes augmentation

**Narcolepsy**

- **definition/clinical features:** excessive daytime sleepiness (all narcolepsy), cataplexy = loss of muscle tone with emotional stimuli (pathognomonic), sleep paralysis (unable to move upon waking for 2-3 min), hypnagogic hallucinations (vivid dreams or hallucinations at sleep onset)
- **epidemiology:** prevalence 1:2000, onset in adolescence/early adulthood; life-long disorder
- **etiology:** presumed autoimmune attack on orexin/hypocretin system, post head injury, multiple sclerosis, hypothalamic tumours; rarely familial
- **diagnosis:** based on clinical history + multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps
- **treatment:**
  - sleep hygiene and scheduled brief naps, restricted driving
  - alerting agents modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
  - anti-cataplectic: TCAs, SSRIs, sodium oxybate

**Parasomnias**

- **definition/clinical features:** unusual behaviors in sleep with clinical features appropriate to stage of sleep
- **etiology:** in elderly, REM sleep behavior disorder may be associated with Parkinson's disease; in children slow wave sleep arousals (sleep walking) may be associated with sleep disordered breathing
- **diagnosis:** clinical history in children, polysomnography in adults to exclude nocturnal seizures
- **treatment:** behavioral management (safety, adequate sleep); clonazepam for REM sleep behavior, tonsillectomy if appropriate in children

**Circadian Rhythm**

- **definition/clinical features:** abnormalities based on time of day rather than sleep (i.e. jet lag, shift work)
- **diagnosis:** clinical history

## CNS Infections

- see [Infectious Diseases](#), ID19



## Spinal Cord Syndromes

- see [Neurosurgery](#), NS28



# Stroke

## Terminology

- **stroke**: sudden onset of neurological deficits of a vascular basis with infarction of CNS tissue
  - infarction is permanent tissue injury (confirmed by neuroimaging)
- **transient ischemic attack (TIA)**: sudden onset of neurological deficits of a vascular basis without infarction (i.e. resolution)

## Pathophysiology

- two major types: ischemic (~80%) and hemorrhagic (~20%)

### 1. Ischemic

- **arterial thrombosis**: thrombus formation in artery (local/in situ)
  - ♦ **large vessel**: stenosis or occlusion of the internal carotid artery, vertebral, or intracranial arteries
    - mechanisms:
      - insufficient blood flow beyond lesion (hemodynamic stroke)
      - underlying processes: atherosclerosis (most common cause), dissection and vasculitis
  - ♦ **small vessel/lacunar**
    - mechanism: chronic hypertension and diabetes cause vessel wall thickening and decreased luminal diameter
    - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule and thalamus)
- **cardioembolic**: blockage of cerebral arterial blood flow due to particles originating from a cardiac source
  - ♦ atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
- **systemic hypoperfusion** (global cerebral ischemia)
  - ♦ inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest, arrhythmia or MI)
  - ♦ primarily affects watershed areas (between the major cerebral arterial territories)

### 2. Hemorrhagic

- **intracerebral hemorrhage (ICH)**
  - ♦ mechanisms:
    - hypertensive (most common): rupture of small microaneurysms (Charcot-Bouchard aneurysms) causing intraparenchymal hemorrhage
      - most common sites: putamen, thalamus, cerebellum, and pons
    - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, vasculitis, drug use (cocaine or amphetamines)
- **subarachnoid hemorrhage (SAH)** see [Neurosurgery](#), NS18

### Stroke Syndromes According to Vascular Territory

- **ACA**: contralateral leg paresis and sensory loss
- **MCA**: proximal occlusion involves:
  1. contralateral weakness and sensory loss of face and arm
  2. cortical sensory loss
  3. may have contralateral homonymous hemianopia or quadrantanopia
  4. if left hemisphere: aphasia
  5. if right hemisphere: neglect
  6. eye deviation towards the side of the lesion and away from the weak side
- **PCA**:
  1. contralateral hemianopia or quadrantanopia
  2. midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  3. thalamic findings: sensory loss, amnesia, decreased level of consciousness
  4. if bilateral: cortical blindness or prosopagnosia
- **basilar artery** (locked-in syndrome):
  1. quadriparesis
  2. dysarthria
  3. impaired eye movements
- **PICA (lateral medullary or Wallenberg syndrome)**: ipsilateral ataxia, ipsilateral Horner's, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, nausea/vomiting, dysphagia, dysarthria, hiccups
- **medial medullary infarct (anterior spinal artery, which can be associated with anterior cord infarct)**: contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness



#### Hypertension Encephalopathy

Acute severe HTN (typically dBp >130 or sBP >200) can cause hypertensive encephalopathy – abnormal fundoscopic exam (papilledema, hemorrhages, exudates, cotton-wool spots), focal neurologic symptoms, nausea, vomiting, visual disturbances and change in LOC.



Early seizure activity occurs in 5-25% of patients after ICH.



Consider transfer of acute stroke patient to a designated stroke centre for neuroprotective or thrombolytic therapy if the patient is seen in first few hours.



Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can also have seizures, focal neurological deficits, or cranial nerve palsies. This is diagnosed with MRV or CTV. Treatment is typically anticoagulation with heparin initially, then transition to warfarin.



20-40% of patients with ischemic stroke may develop hemorrhagic transformation within 1 wk after the initial infarction.

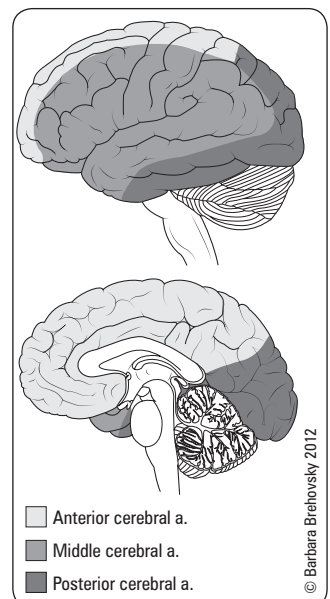


Figure 24. Vascular territories

- **lacunar infarcts (deep hemispheric white matter):**
  - pure motor hemiparesis: posterior limb of internal capsule: contralateral arm, leg, and face
  - pure sensory loss: thalamic: hemisensory loss
  - ataxic hemiparesis: ipsilateral ataxia and leg paresis
  - dysarthria-clumsy hand syndrome: dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness



Bloodwork should only delay treatment if: patient is on anti-coagulants, low Ptt count suspected, abnormal electrolytes suspected or any bleeding abnormality suspected.



Suspect an alternate diagnosis if: fever, decreased LOC, fluctuating symptoms, gradual onset, no focal neurological symptoms, and/or positive symptoms.



Infarcted area of brain tissue can often appear normal on CT during the first several hours after the onset of stroke.



**Aspect Score:** 10-point quantitative score to assess ischemic changes on CT scan

- 10/10 is normal and <4/10 signifies high risk of bleed with rtPA
- Subtract 1 point for each of following structures if abnormal within the ischemic hemisphere: caudate, lentiform, insula, internal capsule, MCA 1, 2, 3, 4, 5, 6 regions.



If rtPA given at stroke onset, delay acute antiplatelet/anticoagulation treatment by 24 h.



The **National Institute of Health Stroke Scale (NIHSS)** is a standardized clinical examination that determines the severity of an acute stroke. It can also be used to monitor response to treatment over time.

The scale uses 11 items that evaluate:

- Level of consciousness
- Visual system
- Motor system
- Sensory system
- Language abilities

Scoring (x/42):

- 0=no stroke
- 1-4=mild stroke
- 5-15=moderate stroke
- 15-20=moderate to severe stroke
- 21-42=severe stroke

rtPA should be considered if score 6 or greater.



**Absolute Contraindications to rtPA**

Hx: improving sx, minor sx, seizure at stroke onset, recent major surgery (within 14 d) or trauma, recent GI or urinary hemorrhage (within 21 d), recent LP or arterial puncture at noncompressible site, PMHx ICH, sx of SAH/pericarditis/MI, pregnancy.

P/E: sBP ≥185, dBP ≥110, aggressive Rx to decrease BP, uncontrolled serum glucose, thrombocytopenia.

Ix: hemorrhage or mass on CT, high INR or aPTT.

## Assessment and Treatment of Ischemic Stroke

### General Assessment

- ABCs, full vital sign monitoring, check glucose, urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis)
- history
  - onset: time when last known to be awake and symptom free
  - mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
- investigations:
  - non-contrast CT head (STAT): to rule out hemorrhage and assess extent of infarct
  - ECG: to rule out atrial fibrillation (cardioembolic cause)
  - CBC, electrolytes, creatinine, PTT/INR, blood glucose
- imaging (i.e. CT) signs of stroke:
  - loss of cortical white-grey differentiation
  - sulcal effacement (i.e. mass effect decreases visualization of sulci)
  - hypodensity of parenchyma
  - insular ribbon sign
  - hyperdense MCA sign

### ACUTE STROKE MANAGEMENT

#### 1. Thrombolysis

- **rtPA** (recombinant tissue plasminogen activator)
- given **within 4.5 h** of acute ischemic stroke onset provided there are clinical indications and no contraindications to use:
- indications: based on NIH Stroke Scale (NIHSS – see sidebar)
- contraindications: see sidebar

#### 2. Anti-Platelet Therapy

- give at presentation of TIA or stroke if rtPA not received
- antiplatelet agents:
  - ASA: recommended dose 81 mg chewed
  - if patient intolerant to ASA, use other antiplatelet agent (i.e. clopidogrel)

#### 3. Acute Anti-Coagulant Therapy

- for patients with TIA or stroke and atrial fibrillation if rtPA not received
  - recommend IV heparin (or ensuring INR between 2-3 if already anticoagulated on warfarin)

### Other Acute Management Issues

- avoid hyperglycemia which can increase the infarct size
- lower temperature if febrile
- prevent complications:
  - NPO if dysphagia (to be reassessed by SLP)
  - DVT prophylaxis if bed-bound
  - initiate rehabilitation early

### Blood Pressure Control

- do **NOT** lower the blood pressure unless the hypertension is severe
  - antihypertensive therapy is withheld for at least 5 d after thromboembolic stroke unless sBP >220 mmHg or dBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection
- acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
- most patients with an acute cerebral infarct are initially hypertensive and their BP will fall spontaneously within 1-2 d
- IV labetalol first-line if needed

### Etiological Diagnosis

- further investigations:
  - additional neuroimaging (MRI)
  - vascular imaging: CTA/MRA/carotid dopplers
  - cardiac tests: ECHO, holter monitoring
  - correct etiological diagnosis is critical for appropriate secondary prevention strategies



## Primary and Secondary Prevention of Ischemic Stroke

### Anti-Platelet Therapy

- primary prevention
  - current evidence has not firmly established a protective role for antiplatelet agents for low-risk patients without a prior stroke/TIA
- secondary prevention
  - ASA is the initial antiplatelet of choice for stroke prevention
  - other agents (generally reserved for those who suffer cerebrovascular symptoms while on ASA or in unable to tolerate ASA)
    - ♦ Aggrenox® (ESPRIT trial)
    - ♦ clopidogrel (CAPRIE trial)
  - there is no benefit (and increased risk of major bleeding) to combining ASA and clopidogrel (MATCH and CHARISMA trials)

### Carotid Stenosis

- primary prevention (asymptomatic)
  - carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per year; carotid endarterectomy reduces the risk of stroke by 1% per year (but 5% risk of complications)
- secondary prevention (previous stroke/TIA in carotid territory)
  - carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%), and is less beneficial for those with symptomatic moderate stenosis (50-69%) (NASCET trial), see [Neurosurgery](#), NS25
- according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI and death. However, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI

### Atrial Fibrillation

- primary and secondary prevention with anticoagulation
  - risk stratification using CHADS<sup>2</sup> score (see sidebar)
    - ♦ 0 (very low risk): antiplatelet
    - ♦ 1 (low risk): anticoagulant or antiplatelet – patient specific decision
    - ♦ >2 (mod-high risk): anticoagulant
  - anticoagulation therapy
    - ♦ warfarin (titrate to INR 2-3)
    - ♦ dabigatran (110 or 150 mg bid) may be an option to warfarin, but should be used cautiously due to lack of a reversal agent should bleeding occur

### Hypertension

- primary prevention
  - targets: BP <140/90 (or <130/80 for diabetics or renal disease)
  - ramipril 10 mg PO OD is effective in patients at high risk for cardiovascular disease (HOPE trial)
    - ♦ ACEI reduce the risk of stroke beyond their antihypertensive effect
- secondary prevention
  - ACEI and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

### Hypercholesterolemia

- primary prevention
  - statins reduce the risk of stroke in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE trial)
- secondary prevention
  - statins reduce risk of subsequent stroke – best evidence is for high dose atorvastatin (SPARCL trial) but lower doses may be more appropriate if patient cannot tolerate high dose

### Diabetes

- ideal management: HbA1c <7%, fasting blood glucose between 4 and 7

### Smoking

- primary prevention
  - smoking increases risk of stroke in a dose-dependent manner
- secondary prevention
  - after smoking cessation, the risk of stroke decreases to baseline within 2-5 yr



#### tPA in Acute Stroke – NINDS Trial

*NEJM* 1995;333:1581-1588

**Study:** Randomized, double-blind, placebo-controlled trial (3 mo follow-up).

**Patients:** 624 patients (mean age 76 yr) with ischemic stroke of recent onset, and no evidence of intracranial hemorrhage on CT. Exclusions included hx of recent stroke or recent surgery, sBP >185, dBP >110, symptoms of SAH, recent GI or GU hemorrhage, seizure with onset of stroke, and recent use of anticoagulants.

**Intervention:** IV tPA or placebo within 180 min of the onset of symptoms.

**Outcomes:** Neurologic deficit at 24 h (NIHSS scale) and functional outcome at 3 mo.

**Results:** There was no significant difference between groups at 24 h. At 3 mo, there were more patients in the tPA group with minimal or no disability (50% vs. 38%, p=0.03). Intracerebral hemorrhage was more common in the tPA group (p<0.001). There was no difference in mortality.

**Conclusion:** IV tPA given within 3 h of onset of acute ischemic stroke improves functional outcome at 3 mo. The risk of intracerebral bleeding is increased.

**Addendum:** When re-assessed at 12 mo from the time of treatment, patients in the tPA group were 30% more likely to have minimal or no disability, with no significant difference in mortality or rate of recurrent stroke (*NEJM* 1999;340:1781-1787).



#### Dabigatran vs. Warfarin in Patients with Atrial Fibrillation (The RE-LY Trial)

*NEJM* 2011; 365:883-891

**Study Type:** Prospective, multi-center RCT. Double-blinded between different doses of dabigatran, unblinded comparison between dabigatran and warfarin.

**Population:** 18,113 patients with atrial fibrillation and a risk of stroke followed over 2 yr.

**Primary Outcome:** Stroke or systemic embolism.

**Results:** Rates of outcome were 1.69% per year in warfarin group and 1.53% per year in dabigatran group (RR 0.91, P <0.001 for non-inferiority).

Minor bleeds were slightly increased in warfarin group (3.36% versus 2.71% with dabigatran; P = 0.003). Risk of hemorrhagic stroke was lower with dabigatran (0.12% versus 0.38%; P <0.001).

**Conclusions:** Dabigatran at 110 mg PO bid was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage compared to warfarin in patients with atrial fibrillation. The 150 mg PO bid dose of dabigatran was more effective at stroke prevention and had a similar bleeding risk to warfarin.



#### High-dose Atorvastatin after Stroke or Transient Ischemic Attack (SPARCL trial)

*NEJM* 2006;355:549-559

**Method:** Multicenter double-blind RCT

**Population:** 4731 patients with stroke or TIA within 1-6 mo before study entry, LDL 100-190 mg/dL, no coronary heart disease.

**Intervention:** 80 mg atorvastatin PO OD or placebo.

**Outcome:** First non-fatal or fatal stroke over 5 yr

**Results:** Patients receiving atorvastatin had a lower rate of stroke (ARI 2.2%, hazard ratio 0.84; P = 0.03). There was a five-yr absolute reduction in risk of 3.5% (P=0.002). There was no significant change in mortality rate, but a small significant increase in the risk of hemorrhagic stroke.

**Conclusions:** High-dose atorvastatin decreases overall incidence of strokes and cardiovascular events in patients with a history of recent stroke or TIA.



#### CHADS<sup>2</sup>

Stroke risk stratification for patients with atrial fibrillation

Congestive heart failure (1 point)

Hypertension sBP >160 mmHg/treated hypertension (1 point)

Age >75 yr (1 point)

Diabetes (1 point)

Prior Stroke or TIA (2 points)



### Physical Activity

- regular physical activity is an important lifestyle measure in stroke prevention and its beneficial effect has a dose-related response in terms of intensity and duration of activity

### Stroke Rehabilitation

- individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

## Cerebral Hemorrhage

### Investigations

- general investigations, see *Assessment and Treatment of Ischemic Stroke*, N44
- further investigations:
  - lumbar puncture (if suspect subarachnoid hemorrhage despite negative CT)
  - may require cerebral angiogram if suspect aneurysm or AVM
  - if typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion

### Management

- medical
  - anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2010 AHA/ASA guidelines suggest that reducing sBP to as low as 140 mmHg with IV anti-hypertensives is safe and appropriate management (target BP 140-160 systolic)
  - ICP lowering medical management (if necessary): see *Neurosurgery*, NS7
- surgical: see *Neurosurgery*, NS19

## Multiple Sclerosis (MS)



### Definition

- a chronic inflammatory disease of the CNS characterized by relapsing remitting, or progressive neurologic symptoms due to inflammation, demyelination and axonal degeneration

### Clinical Patterns of MS (Figure 25)

- relapsing remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- most RRMS goes on to become SPMS

### MS Variants

- Devic's = neuromyelitis optica (NMO):** severe optic neuritis and extensive transverse myelitis extending >3 vertebral segments (NMO antibody positive)
- clinically isolated syndrome (CIS):** single MS-like episode, which may progress to MS
- tumefactive MS:** solitary lesion >2 cm mimicking neoplasms on MRI
- fulminant MS (Marburg):** rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- acute disseminated encephalomyelitis (ADEM):** monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children often following infection or vaccination

### Etiology

- genetic
  - polygenetic: the HLA-DRB1 gene has been demonstrated to be a genetically susceptible area
  - 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
- environmental
  - MS is more common in regions with less sun exposure and lower stores of vitamin D (Europe, Canada, US, New Zealand, SE Australia)
  - MS has also been linked to certain viruses (EBV is associated with MS)

### Epidemiology

- onset 17-35 yr; 3F:1M
- PPMS occurs in an older population with 1F:1M



### ABCD<sup>2</sup> Score

To predict/identify individuals at high risk of stroke following TIA

**Age:** 1 point for age >60 yr

**Blood pressure (at presentation):**

1 point for hypertension

(>140/90 mmHg at initial evaluation)

**Clinical features:** 2 points for unilateral weakness, 1 for speech disturbance without weakness

**Duration of symptoms:** 1 point for 10-59 min, 2 points for >60 min

**Diabetes:** 1 point

**Stroke risk:** Scores 0-3: low risk, 4-5: moderate risk, 6-7: high risk



Carotid endarterectomy needs to be done within 2 wk of the ischemic event for the most benefit.



### ACE Inhibitor in Stroke Prevention – HOPE Trial

*NEJM* 2000;342:145-153

**Study:** Randomized, blinded, placebo-controlled trial. Mean follow-up 5 yr.

**Patients:** 9297 patients 55 yr of age or older (mean age 66 y, 73% men) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure.

**Intervention:** Ramipril 10 mg daily orally vs. matching placebo.

**Main Outcomes:** Stroke, MI, or death from cardiovascular causes

**Results:**

Outcome	RRR (95%CI)	NNT (CI)
Stroke	32% (16 to 44)	67 (43 to 145)
MI, stroke, or CV mortality	22% (14 to 30)	26 (19 to 43)
All-cause mortality	16% (5 to 25)	56 (32 to 195)

Treatment with ramipril reduced the risk of stroke (3.4 percent vs. 4.9 percent; RR 0.68;  $p < 0.001$ ).

**Conclusions:** In adults at high risk for cardiovascular events, ramipril reduced the risk of stroke, as well as other vascular events and overall mortality.

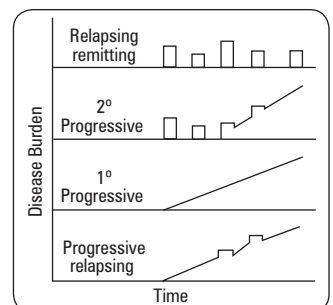


Figure 25. Clinical patterns of MS



### Chronic Cerebrospinal Venous Insufficiency (CCSVI)

A theory proposed in 2008 describing abnormal venous blood flow in patients with MS. Highly controversial theory currently being investigated.

## Diagnosis

- dissemination in space and in time as based on the revised McDonald criteria
  - dissemination in time: 2 or more attacks, new gadolinium enhancing lesion 3 mo later, or new T2 lesions >1 mo after first attack
  - dissemination in space: clinical evidence of 2 or more lesions; or three of [1 gadolinium enhancing or 9 T2 lesions], [1 infratentorial lesion], [1 juxtacortical lesion], [3 periventricular lesions]

## Clinical Features

- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. INO), impaired gait, vertigo, bladder dysfunction
- Lhermitte's sign:** flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- Uhthoff's phenomenon:** worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically weakness of legs in pyramidal distribution paired with cerebellar findings of arms (i.e. intention tremor)
- symptoms not commonly found in MS: visual field defects, aphasia, apraxia, progressive hemiparesis
- relapse: acute/subacute onset of clinical dysfunction that peaks from days to weeks, followed by remission with variable symptom resolution (symptoms must last at least 24 h)
- in RRMS, average 0.4 to 0.6 relapses/yr, but higher disease activity in first year of disease

## Investigations

- MRI:** demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
  - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxta cortical region, and dorsolateral spinal cord
  - Dawson's fingers: periventricular lesions extending into corpus callosum
  - cranial MRI is more sensitive than spinal MRI
- CSF:** oligoclonal bands in 90%, increased IgG concentration
- evoked potentials (visual/auditory/somatosensory):** delayed but well-preserved wave forms

## Treatment

- acute treatment:** methylprednisolone 1000 mg IV daily x 3-7 d (no taper required); if poor response to corticosteroids may consider plasma exchange
- disease modifying therapy (DMT):**
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: interferon- $\beta$  (injection: Betaseron®, Avonex®, Rebif®), glatiramer acetate (injection: Copaxone®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion)
  - new oral agents: fingolimod (available) and cladribine (not yet available)
    - indications for fingolimod: newly diagnosed patients with active RRMS who prefer oral treatment despite increased risks or those intolerant of first line therapies
  - CIS: early treatment with interferons may delay potential second attack
  - RRMS: DMT reduces rate of relapse by about 30%
  - PPMS/SPMS: no proven efficacy of DMTs
- symptomatic treatment**
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantidine, modafinil, methylphenidate
  - depression: antidepressant, lithium
  - constipation: high fibre intake, stool softener, laxatives
  - sexual dysfunction: sildenafil, tadalafil, vardenafil
- education and counseling:** MS society, support groups, psychosocial issues

## Prognosis

- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy



Most symptoms in MS are due to cord, brainstem and optic nerve lesions.



The Expanded Disability Status Scale (EDSS) is used as a measure of disability progression and is scored from 0 to 10 based on the neurologic exam and ambulation.



**Recombinant Interferon Beta or Glatiramer Acetate for Delaying Conversion of the First Demyelinating Event to Multiple Sclerosis**  
*Cochrane DB Syst Rev* 2008;2:CD005278  
**Study:** Meta-analysis of RCTs of clinically isolated syndrome (CIS) patients treated with immunomodulatory drugs.

**Primary Outcomes:** Proportion of patients converting to clinically definite MS and adverse effects.

**Results:** Three trials (n=1160) tested the efficacy of interferon (IFN $\beta$ ) and no trial tested glatiramer acetate (GA). A pooled odds ratio (OR) of 0.53 (5% CI, 0.40-0.71,  $p < 0.0001$ ) for patients on IFN versus placebo at one year. Two year follow-up odds ratio was 0.52 (95% CI 0.38-0.70,  $p < 0.0001$ ). There was no significant increase in adverse events for those on IFN $\beta$ .

**Conclusions:** IFN $\beta$  treatment can delay progression to clinically definite MS in patients with CIS over two years.



**Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis**  
*NEJM* 2010;362:402-415

**Method:** Multicenter double-blind RCT.

**Population:** 1292 patients with relapsing-remitting MS and at least one relapse.

**Intervention:** Oral fingolimod at 0.5-1.25 mg or 30  $\mu$ g IM interferon- $\beta$ .

**Outcomes:** Annualized relapse rate over 1 yr; lesions on T2-weighted MRI.

**Results:** Annualized relapse rate was lower in both groups receiving fingolimod compared to interferon: 0.20 (95% CI 0.16-0.26) with 1.25 mg fingolimod, 0.16 (95% CI 0.12 to 0.21) with 0.5 mg fingolimod, 0.33 with interferon (95% CI 0.26-0.42;  $P < 0.001$ ). MRI findings also showed greater reduction of lesions in fingolimod-treated patients. Progression of disability was unchanged. Side effects included severe infections like HSV encephalitis, disseminated VZV, other HSV infections, and skin cancer.

**Conclusions:** Oral fingolimod is superior to interferon  $\beta$  injections in reducing relapses and MRI lesion load in patients with MS.

## Common Medications

Table 25. Common Medications – Major issues

Indications	Mechanism of Action/Class	Generic Name	Trade Name	Dosing	Contraindications	Side Effects
Parkinson's disease	Dopamine precursor	levodopa + carbidopa	Sinemet®	Carbidopa 25 mg/levodopa 100 mg PO tid Maximum 200 mg carbidopa and 2000 mg levodopa per day	Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions	Nausea, hypotension, hallucinations, dyskinesias in last 14 d, history of melanoma or undiagnosed skin lesions
	Dopamine agonist	bromocriptine	Parlodel®	1.25 mg PO bid, increase by 2.5 mg/d q2-4wk, up to 10-30 mg PO tid	Concomitant use of potent inhibitors of CYP3A4, uncontrolled hypertension, ischemic heart disease, peripheral vascular disease. Caution with renal or hepatic disease	Hypotension, nausea, dizziness, constipation, diarrhea, vomiting, abdominal cramps, headache, nasal congestion, drowsiness, hallucinations
	MAO B inhibitor	selegiline	Eldepryl®	5 mg PO bid	Concomitant use of meperidine or tricyclic antidepressants	Headache, insomnia, dizziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinesia, risk of hypertensive crisis with tyramine-containing foods
Myasthenia gravis	Acetylcholinesterase inhibitor	pyridostigmine	Mestinon®	600 mg/d PO divided in 5-6 doses Range 60-1500 mg/d	GI or GU obstruction	Nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness
Acute migraine	Triptan (selective 5-hydroxytryptamine receptor agonist)	sumatriptan	Imitrex®	25-100 mg PO prn, maximum 200 mg/d	Hemiplegic/basilar migraine, ischemic heart disease, cerebrovascular disease, uncontrolled hypertension, use of ergotamine/5-HT <sub>1</sub> agonist in past 24 h, use of MAO inhibitor in last 14 d, severe hepatic disease	Vertigo, chest pain, flushing, sensation of heat, hypertensive crisis, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, nausea, vomiting, headache, hyposalivation, fatigue
	Ergot (5-HT <sub>1D</sub> receptor agonist)	dihydroergotamine	Migranal®	Nasal spray 0.5 mg/spray, maximum 4 sprays/d	Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled hypertension, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction, use of triptans in last 24 h, use of MAO inhibitors in last 14 d	Coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation. May cause significant rebound headache
Migraine prophylaxis	Anticonvulsant	topiramate	Topamax®	25 mg OD PO (in evening); may increase weekly by 25 mg/d to a max 50 mg bid		Sedation, mood disturbance, cognitive dysfunction, anorexia, nausea, diarrhea, paresthesias, metabolic acidosis, glaucoma, SJS/TEN
	β-blocker	propranolol	Inderal®	80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q6-8h	Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma	Fatigue, cognitive dysfunction, disturbed sleep, rashes, dyspepsia, dry eyes, heart failure, bronchospasm, risk of acute tachycardia and HTN if withdrawal
Epilepsy	Anticonvulsant for partial ± 2° generalization, generalized tonic-clonic	carbamazepine	Tegretol® (Carbatrol)	Start at 100-200 mg PO OD-bid, increase by 200 mg/d up to 800-1200 mg/d	History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d	Drowsiness, headache, unsteadiness, dizziness, n/v, skin rash, agranulocytosis/aplastic anemia (rare)
	Anticonvulsant for partial, tonic-clonic, status epilepticus	phenytoin	Dilantin®	100 mg PO tid, maintenance dose up to 200 mg PO tid SE: 10-15 mg/kg IV loading dose then maintenance doses of 100 mg PO or IV q6-8h	Hypersensitivity, pregnancy, breast-feeding; caution with P-450 interactions	Hypotension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, headache, blood dyscrasias, nystagmus, n/v, constipation, sedation, teratogenic
	Anticonvulsant for partial or generalized, absence seizures	valproic acid	Depacon® Depakene® Depakote®	10-15 mg/kg/d PO, increase incrementally until therapeutic dose to max of 60 mg/kg/d	Hypersensitivity, hepatic disease, urea cycle disorders	Hepatic failure, headache, somnolence, alopecia, n/v, diarrhea, tremor, diplopia, thrombocytopenia, hypothermia, pancreatitis, encephalopathy
	Anticonvulsant for absence seizures	ethosuximide	Zarontin®	500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses	Hypersensitivity (succinimides)	CNS depression, blood dyscrasias, SLE, SJS, GI symptoms

**Table 25. Common Medications – Major issues (continued)**

Indications	Mechanism of Action/Class	Generic Name	Trade Name	Dosing	Contraindications	Side Effects
<b>Stroke prevention in AF</b>	Anticoagulant (direct thrombin inhibitor)	dabigatran	Pradax®	110 mg PO bid or 150 mg PO bid	CrCl <30 mL/min, significant hemostatic impairment or CNS lesions within 6 mo with high risk of bleeding	Dyspepsia, gastritis, bleeding
<b>Mild to moderate AD or DLB</b>	Cholinesterase Inhibitor	donepezil	Aricept®	5 mg PO OD, may increase to 10 mg PO OD after 4-6 wk	Hypersensitivity to donepezil or to piperidine derivatives	Diarrhea, n/v, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block
<b>Multiple sclerosis</b>	MS Disease Modifying Therapy	interferon-β-1b interferon-β-1a SC interferon-β-1a IM	Betaseron® Rebif® Avonex®	0.25 mg (8 MU) SC every other day 44 µg SC 3 times/wk 30 µg IM once weekly	Pregnancy, hypersensitivity to natural or recombinant interferon β	Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time)
	MS Disease Modifying Therapy	glatiramer acetate	Copaxone®	20 mg SC OD	Hypersensitivity to glatiramer or mannitol	Injection site reactions, nausea, transient chest pain, vasodilation
	MS Disease Modifying Therapy	natalizumab	Tysabri®	300 mg IV given over 1 h, every 4 wk	Hypersensitivity to natalizumab, progressive multifocal leukoencephalopathy (PML)	Rash, nausea, arthralgia, headache, infections, rare risk of PML and melanoma
	MS Disease Modifying Therapy	fingolimod	Gilenya®	0.5 mg PO OD	Not available	Diarrhea, transaminitis, headache, bradyarrhythmia, lymphocytopenia
<b>Spasticity (i.e. MS)</b>	Muscle Relaxant – Antispastic	baclofen	Lioresal®	5 mg PO tid, increase by 15 mg/d q3d to max dose 80 mg/d in three divided doses	Hypersensitivity to baclofen	Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea

## Landmark Neurology Trials

Trial	Reference	Results
CREST	<i>NEJM</i> 2010; 363:11-23	Carotid stenting and endarterectomy had similar benefits in reduction of stroke, MI and death in carotid stenosis, but in the periprocedural period, stenting had a higher rate of stroke, while endarterectomy had a higher rate of MI
ECASS 3	<i>NEJM</i> 2008; 359:1317-29	rtPA improved clinical outcomes when administered within 3 to 4.5 h of acute ischemic stroke
Interferon- $\beta$ Multiple Sclerosis Study Group Trial	<i>Neurology</i> 1993; 43:655-61	Interferon- $\beta$ -1b reduces relapse rate and severity of relapses in RRMS
NASCET	<i>NEJM</i> 1991; 7:445-53	Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy
NINDS rtPA	<i>NEJM</i> 1995; 333:1581-7	rtPA reduces mortality and long-term disability when administered within 3 h of acute stroke
PROFESS	<i>NEJM</i> 2008; 359:1238-51	ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention
RELY	<i>NEJM</i> 2009; 361:1139	Dabigatran superior to warfarin for stroke prevention in patients with atrial fibrillation
SPARCL	<i>NEJM</i> 2006; 355:549-59	The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA

## References

### Coma

Bhidayasiri R, Waters MF, Giza CC. Neurological differential diagnosis: a prioritized approach. Massachusetts: Blackwell Publishing, 2005. p71-2.  
Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL (editors). Harrison's principles of internal medicine, 16th ed. Toronto: McGraw-Hill Companies, 2005. p1629-1630.

### Common Presenting Complaints

Bhidayasiri R, Waters MF, Giza CC. Neurological differential diagnosis: a prioritized approach. Massachusetts: Blackwell Publishing, 2005. p12-13, 305-14.

### Headache

Chronicle EP, Mulleners WM. Anticonvulsant drugs for migraine prophylaxis. Cochrane DB Syst Rev 2009;CD003226.  
Detsky, ME, McDonald DR, Baerlocher MQ, et al. Does this patient with headache have a migraine or need neuroimaging. *JAMA* 2006;296:1274-1283.  
Francis GJ, et al. Acute and preventive pharmacologic treatment of cluster headache. *Neurology* 2010;75:463-473.  
Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd ed. Cephalalgia 2004;24(S1):9-160.  
Oldman AD, Smith LA, McQuay HJ, et al. Pharmacological treatments for acute migraine: quantitative systematic review. *Pain* 2002;97:247-57.  
Silberstein SD, et al. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review). *Neurology* 2000;55:754-62.

### Traumatic Brain Injury

Anderson-Barnes VC, Weeks SR, Tsao JW. Mild traumatic brain injury update. *Continuum* 2010;16(6):17-23.

### Movement Disorders

Bayard M, Avonda T, Wadzinski J. Restless legs syndrome. *Am Fam Physicia*. 2008; 78:235-40.  
Centers for Disease Control and Prevention (CDC). Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. *MMWR Recomm Rep* 2004;53(RR-4):1-33.  
England JD, Gronseth G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). *Neurology* 2009;72:185-92.  
Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181-4  
Stowe RL, Ives NJ, Clarke C, et al. Dopamine agonist therapy in early Parkinson's disease. *Cochrane DB Syst Rev* 2008;CD006564.

### Multiple Sclerosis

Ambati BK, Smith WT, Azer-Bentsianov MT. Residents manual of medicine. Hamilton: BC Decker, 2001. p211-13.  
Carpenter CCJ, Griggs RC, Loscalzo J, eds. Cecil essentials of medicine, 5th ed. Philadelphia: WB Saunders, 2001. p973-6.  
Clerico M, Faggiano F, Palace J, et al. Recombinant interferon beta or glatiramer acetate for delaying conversion of the first demyelinating event to multiple sclerosis. *Cochrane DB Syst Rev* 2009;CD005278.  
Ferri FF. Practical guide to the care of the medical patient. St. Louis: Mobsy, 2001. p654-656.  
Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *NEJM* 2000;343:938-952.  
Olek MJ, (editor). Multiple sclerosis: etiology, diagnosis, and new treatment strategies. New Jersey: Humana Press, 2005. p36-40, 57, 131, 222-23.  
Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos I, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005;58:840-846.  
Samuels MA, Feske SK, (editors). Office practice of neurology, 2nd ed. Philadelphia: Elsevier Science, 2003. p410-411.  
The TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing MS. *NEJM* 2010;362:402-415.  
Vosoughi R, Freedman MS. Therapy of MS. *Clin Neurol Neurosurg* 2010;112:365-385.

### Epilepsy

Ambati BK, Smith WT, Azer-Bentsianov MT. Residents manual of medicine. Hamilton: BC Decker, 2001. p203-205.  
Ferri FF. Practical guide to the care of the medical patient. St. Louis: Mobsy, 2001. p617-619.  
Griggs RC, Andreoli, Carpenter, Griggs, Benjamin (editors). Cecil essentials of medicine 7th ed. Saunders Elsevier p1120-1128.  
Lowenstein DH, Alldredge BK. Status epilepticus. *NEJM* 1998;338:970-976.

### Spinal Cord Syndrome

Wagner R, Jagoda A. Neurologic emergencies: spinal cord syndromes. *Emerg Medd Clinic N Am* 1997;15:699-711.

**Stroke**

- Adams HP Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. *Stroke* 1993;24:35-41.
- Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and Aspirin® versus Aspirin® alone for the prevention of atherothrombotic events. *NEJM* 2006;354:1706-1717.
- Brott TG, Hobson RW, George H et al. Stenting versus endarterectomy for treatment of carotid stenosis. *NEJM* 2010;363:11-23.
- CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus Aspirin® in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-1339.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *NEJM* 2009;361:1139-1151.
- Diener HC, et al. Aspirin® and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial *Lancet* 2004;364:331-337.
- Frontera W, Silver J. Essentials of physical medicine and rehabilitation. Philadelphia: Hanley and Belfus, 2002. p778-782.
- Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-2870.
- Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;369:283-292.
- Lindsay K, Bone I. Neurology and neurosurgery illustrated. Philadelphia: Churchill Livingstone, 2003. p244.
- Mullins ME, Lev MH, Schellingerhout D, Gonzalez RG, Schaefer PW. Intracranial hemorrhage complicating acute stroke: how common is hemorrhagic stroke on initial head CT scan and how often is initial clinical diagnosis of acute stroke eventually confirmed? *Am J Neuroradiol* 2005;26:2207-2212.
- Stroke Unit Trialists' Collaboration. Organized inpatient (stroke unit) care for stroke. *Cochrane DB Syst Rev* 2009;CD000197.
- Passero S, Rocchi R, Rossi S, Olivelli M, Vatti G. Seizures after spontaneous supratentorial intracerebral hemorrhage. *Epilepsia* 2002;43:1175-80.
- Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, Hu WY, Buchan AM. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *Am J Neuroradiol* 2001;22:1534-42.
- Program early CT score (ASPECTS) for assessing CT scans in patients with acute strokes. *AMJ Neuroradiol* 2001;22:1534-1542.
- The ESPRIT Study Group. Aspirin® plus dipyridamole versus Aspirin® alone after cerebral ischaemia of arterial origin (ESPRIT): randomized controlled trial. *Lancet* 2006;367:1665-1673.
- The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an ACEI, ramipril, on cardiovascular events in high-risk patients. *NEJM* 2000;342:145-153.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *NEJM* 1995;333:1581-1588.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Effects of tissue plasminogen activator for acute ischemic stroke at one yr. *NEJM* 1999;340:1781-1787.

**Pain**

- Chen N, Li Q, Zhang Y, Zhou M, Zhou D, He L. Vaccination for preventing postherpetic neuralgia. *Cochrane DB Syst Rev* 2011;CD007795.
- Coen PG, Scott F, Leedham-Green M, et al. *European Journal of Pain* 2006;10:695-700.
- Marcus, D. (2005). Chronic pain – a primary guide to practical management. New Jersey: Humana Press. p111-28.
- Salinas RA, Alvarez G, Daly F, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane DB Syst Rev* 2010;CD001942.
- Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four yr of experience. *Can Fam Phys* 2010;56:514-517.

**Dementia**

- Feldman HH, Jacova C, Robillard A, Garcia A, Chow T, Borrie M, et al. Diagnosis and treatment of dementia: diagnosis. *CMAJ* 2008;178:825-836.
- Josephs KA, Ahlskog JE, Parisi JE, et al. Rapidly progressive neurodegenerative dementias. *Arch Neurol* 2009;66:201-207.
- McKeith IG, Dickson DW, Lowe J, et al. Consortium on DLB. Diagnosis and management of dementia with lewy bodies: third report of the DLB consortium. *Neurology* 2005;65:1863-1872.
- Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546-1554.
- Patterson C, Feightner JW, Garcia A, Hsiung GY, MacKnight C, Sadvonick AD. Diagnosis and treatment of dementia: risk assessment and primary prevention of alzheimer disease. *CMAJ* 2008;178:548-556.
- Rolinski M, Fox C, Maidment I, et al. Cholinesterase inhibitors for dementia with lewy bodies, Parkinson's disease dementia and cognitive impairment In Parkinson's disease. *Cochrane DB Syst Rev* 2012;CD006504.
- Vigen CL, Mack WJ, Keefe RS, et al. Cognitive effects of atypical antipsychotic medications in patients with alzheimer's disease: outcomes from CATIE-AD. *Am J Psychiatry* 2011;168:831-839.
- Zerr et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2000;55:811-815.
- Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain* 2009;132:2659-2668.

**Movement Disorders**

- Stowe R, Ives N, Clarke CE, et al. Dopamine agonist therapy in early Parkinson's disease. *Cochrane DB Syst Rev* 2009;CD006564.
- England JD, Gronseth GS, Franklin G, et al. Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). *Neurology* 2009;72:185-192.

**General**

- Aminoff MJ, Greenberg DA, Simon RP. Lange: clinical neurology, 6th ed. Toronto: McGraw-Hill.
- Andreoli, Carpenter, Griggs, Benjamin. Cecil essentials of medicine, 7th ed. Saunders Elsevier.
- Mumenthaler M, Mattle H. Fundamentals of neurology. Thieme: Stuttgart and New York, 2006.
- Scherokman B, Selwa L, Alguire PC. Approach to common neurological symptoms in internal medicine: AAN core curriculum. 2011.
- Yamada KA, Awadalla S. The Washington manual of medical therapeutics, 31st ed. Lippincott Williams & Wilkins. pp. 531-534.

**Drug Information**

- Compendium of Pharmaceuticals and Specialties 2010. Ottawa: Canadian Pharmacists Association, 2010.
- Lexi-Comp Online™. Hudson: Lexi-Comp, 2011.



Farshad Nassiri and Johnny Nguyen, chapter editors  
 Jieun Kim and Daniel Soong, associate editors  
 Jeff Martin, EBM editor  
 Dr. Todd Mainprize and Dr. Eric Massicotte, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Extradural Lesions</b> . . . . .	<b>24</b>
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	Root Compression	
<b>Differential Diagnoses of Common Neurosurgical Presentations</b> . . . . .	<b>4</b>	Cervical Disc Syndrome	
<b>INTRACRANIAL PATHOLOGY</b>		Cervical Stenosis (Cervical Spondylosis)	
<b>Intracranial Pressure (ICP) Dynamics</b> . . . . .	<b>4</b>	Lumbar Disc Syndrome	
ICP/Volume Relationship		Cauda Equina Syndrome	
Cerebral Blood Flow (CBF)		Lumbar Spinal Stenosis	
ICP Measurement		Neurogenic Claudication	
Elevated ICP		<b>Intradural Intramedullary Lesions</b> . . . . .	<b>28</b>
<b>Herniation Syndromes</b> . . . . .	<b>7</b>	Syringomyelia (Syrinx)	
Treatment of Elevated ICP		<b>Spinal Cord Syndromes</b> . . . . .	<b>28</b>
<b>Hydrocephalus</b> . . . . .	<b>8</b>	<b>Peripheral Nerves</b> . . . . .	<b>29</b>
<b>Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)</b> . . . . .	<b>10</b>	<b>SPECIALTY TOPICS</b>	
<b>Tumours</b> . . . . .	<b>10</b>	<b>Neurotrauma</b> . . . . .	<b>30</b>
Metastatic Tumours		Trauma Assessment	
Astrocytoma		Head Injury	
Meningioma		Brain Injury	
Vestibular Schwannoma (Acoustic Neuroma)		Late Complications of Head/Brain Injury	
Pituitary Adenoma		Spinal Cord Injury (SCI)	
<b>Pus</b> . . . . .	<b>15</b>	Fractures of the Spine	
Cerebral Abscess		Neurologically Determined Death	
<b>Blood</b> . . . . .	<b>16</b>	Coma	
Extradural ("Epidural") Hematoma		Persistent Vegetative State	
Subdural Hematoma (SDH)		<b>Pediatric Neurosurgery</b> . . . . .	<b>35</b>
<b>Cerebrovascular Disease</b> . . . . .	<b>18</b>	Spinal Dysraphism	
Subarachnoid Hemorrhage (SAH)		Intraventricular Hemorrhage (IVH)	
Intracerebral Hemorrhage (ICH)		Hydrocephalus in Pediatrics	
Intracranial Aneurysms		Dandy-Walker Malformation	
Carotid Stenosis		Chiari Malformations	
<b>Vascular Malformations</b> . . . . .	<b>23</b>	Craniosynostosis	
Arteriovenous Malformations (AVMs)		Pediatric Brain Tumours	
Cavernous Malformations		<b>Functional Neurosurgery</b> . . . . .	<b>39</b>
<b>EXTRACRANIAL PATHOLOGY</b>		Movement Disorders	
<b>Approach to Limb/Back Pain</b> . . . . .	<b>24</b>	Neuropsychiatric Disorders	
		Chronic Pain	
		<b>Surgical Management of Epilepsy</b> . . . . .	<b>40</b>
		<b>Surgical Management for Trigeminal Neuralgia</b> . . . . .	<b>41</b>
		<b>Common Medications</b> . . . . .	<b>41</b>
		<b>References</b> . . . . .	<b>42</b>

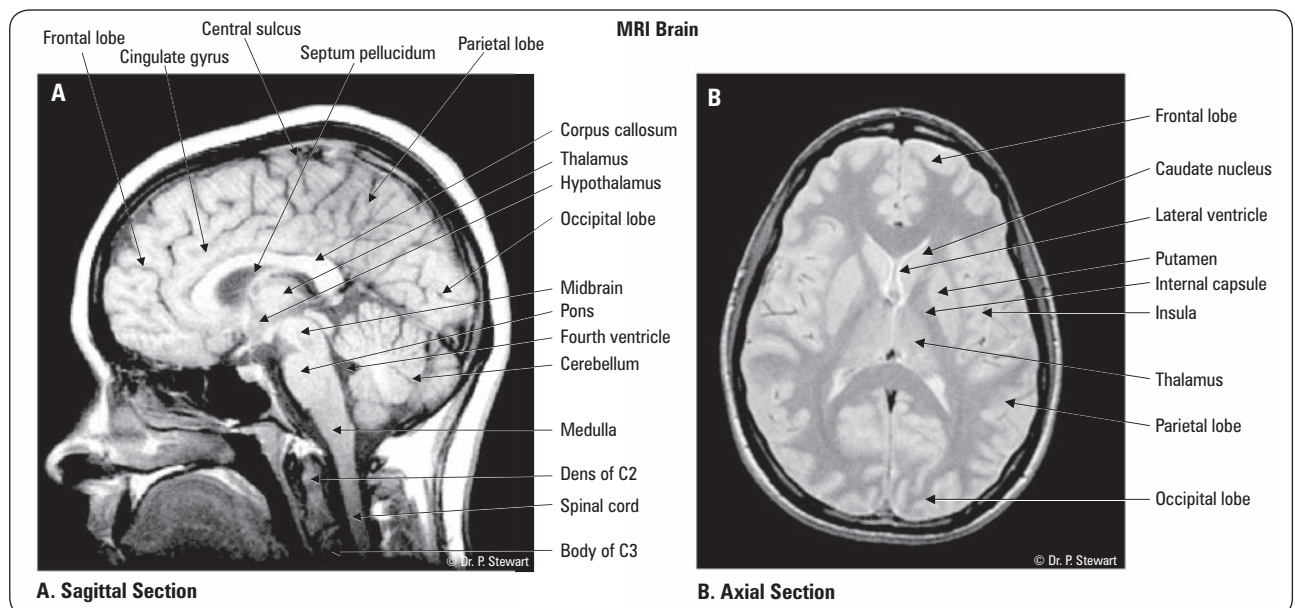
## Acronyms

AVF	arteriovenous fistula	GPI	globus pallidus pars interna	OPLL	ossification of posterior longitudinal ligament
AVM	arteriovenous malformation	H/A	headache	PAG	periaqueductal grey matter
CBF	cerebral blood flow	HTN	hypertension	PET	positron emission tomography
CSF	cerebral spinal fluid	IC	internal capsule	PLL	posterior longitudinal ligament
CPA	cerebellar pontine angle	ICF	intracellular fluid	PVG	periventricular grey matter
CPP	cerebral perfusion pressure	ICP	intracranial pressure	SAH	subarachnoid hemorrhage
CVR	cerebral vascular resistance	IVH	intraventricular hemorrhage	SDH	subdural hemorrhage
DBS	deep brain stimulation	LMN	lower motor neuron	SIADH	syndrome of inappropriate antidiuretic hormone
DI	diabetes insipidus	LOC	loss of consciousness	SPECT	single photon emission computed tomography
ECF	extracellular fluid	LP	lumbar puncture	SRS	stereotactic radiosurgery
ECT	electroconvulsive therapy	MAP	mean arterial pressure	STN	subthalamic nucleus
EEG	electroencephalography	MLS	midline shift	UMN	upper motor neuron
EMG	electromyography	NC	neurogenic claudication	VPL	ventral posterolateral
EVD	external ventricular drain	NPH	normal pressure hydrocephalus	VPM	ventral posteromedial
GCS	glasgow coma scale	N/V	nausea/vomiting		

## Basic Anatomy Review

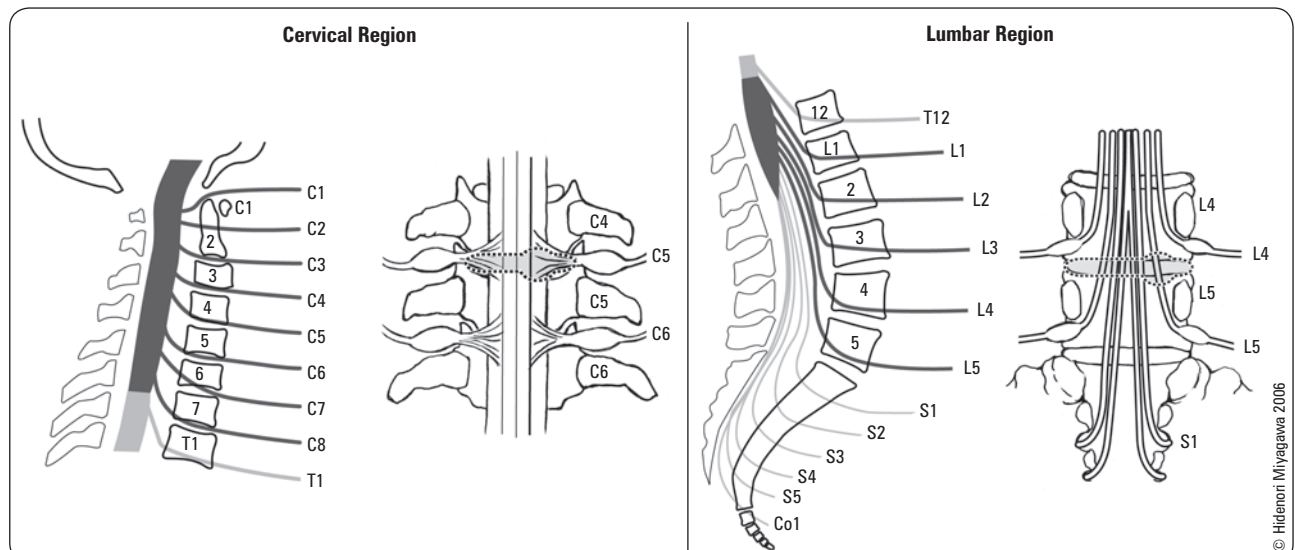


See Functional  
Neuroanatomy Software



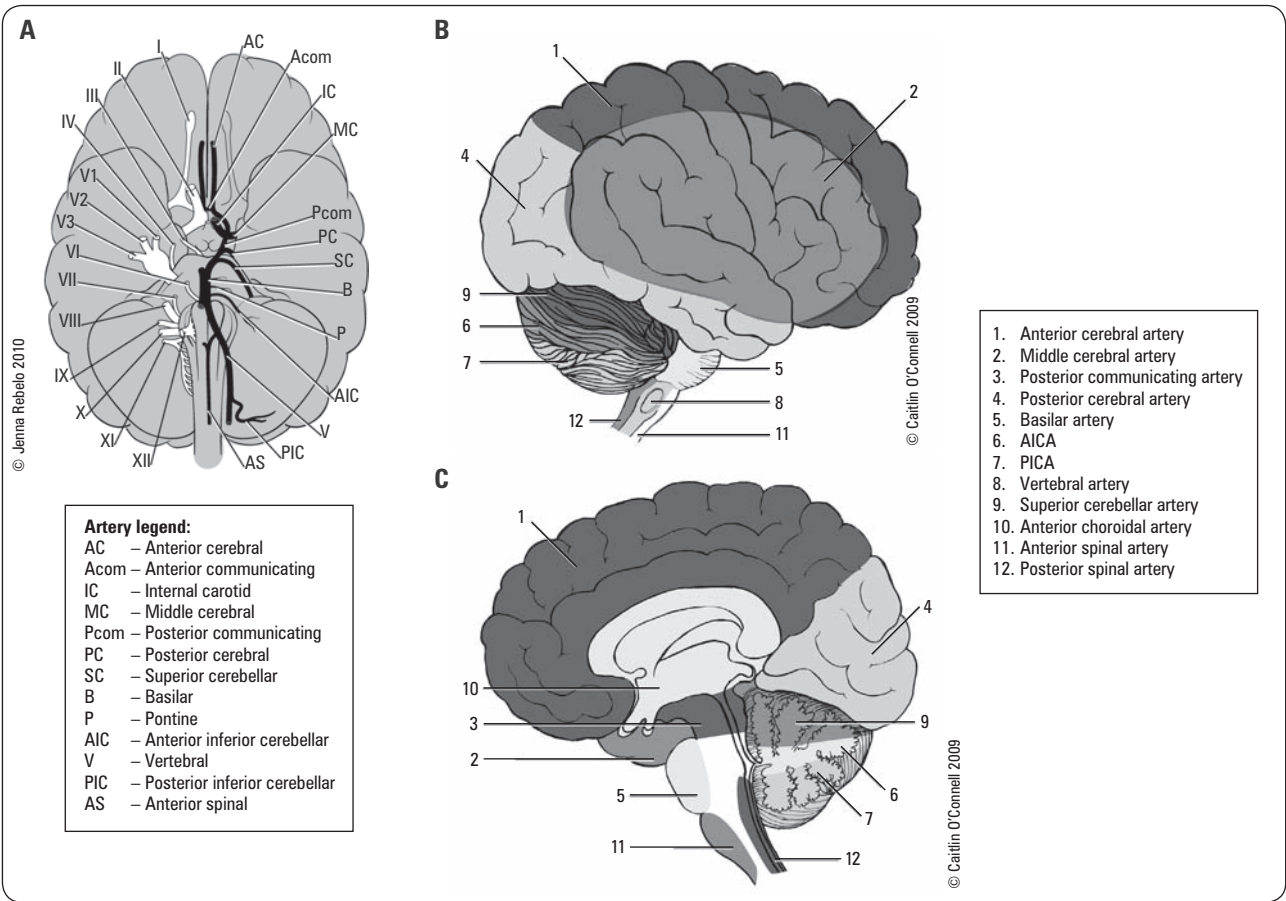
**Figure 1. Magnetic resonance imaging (MRI) neuroanatomy**

From Stewart P et al. Functional Neuroanatomy (Version 2.1). Health Education Assets Library, 2005

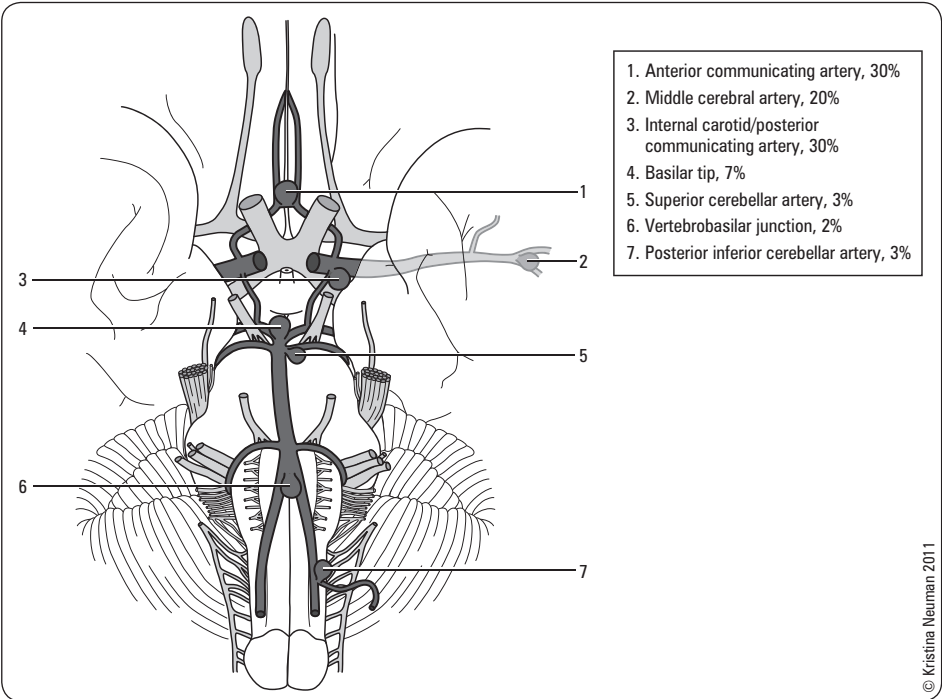


**Figure 2. Relationship of nerve roots to vertebral level in the cervical and lumbar spine**

**Note:** AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement



**Figure 3. Vascular supply of the brain.** Please refer to legend for artery names. 3A. Circle of Willis, most common variant. 3B. Vascular territories of the brain and brainstem, saggital view, seen laterally. 3C. Vascular territories of the brain and brainstem, saggital view, seen medially



**Figure 4. Aneurysms of the Circle of Willis**

## Differential Diagnoses of Common Neurosurgical Presentations

Intracranial Mass Lesions	Disorders of the Spine	Peripheral Nerve Lesions
Tumour Metastasis Astrocytoma Meningioma Vestibular schwannoma (acoustic neuroma) Pituitary adenoma Primary CNS lymphoma	Extradural Degenerative: disc herniation, canal stenosis, spondylolisthesis/spondylolysis Infection/inflammation: osteomyelitis, discitis Ligamentous: ossification of posterior longitudinal ligament (OPLL) Trauma: mechanical compression/instability, hematoma Tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma	Neuropathies Traumatic Entrapments Iatrogenic Inflammatory Tumours
Pus/inflammation Cerebral abscess, extradural abscess, subdural empyema Encephalitis (see <a href="#">Infectious Diseases, ID20</a> ) Tumefactive multiple sclerosis (MS)	Intradural extramedullary Vascular: dural arterio-venous fistula, subdural hematoma (especially if on anticoagulants) Tumours (40% of all spinal tumours): meningioma, schwannoma, neurofibroma	
Blood Extradural (epidural) hematoma Subdural hematoma Ischemic stroke Hemorrhage: SAH, ICH, IVH	Intradural intramedullary Tumours (5% of all spinal tumours): astrocytomas and ependymomas most common; also hemangioblastomas and dermoids	
Cyst	Syringomyelia (common causes: trauma, congenital, idiopathic) Infectious/inflammatory: TB, sarcoid, transverse myelitis Vascular: AVM, ischemia	



## INTRACRANIAL PATHOLOGY

### Intracranial Pressure (ICP) Dynamics

**Table 1. Approach to Intracranial Pathology**

Issue	Time Frame	Features
Vascular	Sudden	No headache = occlusive Headache = hemorrhagic
Metabolic	Hours to days	Affects entire CNS
Infectious	Days to weeks	Often a source of infection on history
Tumour	Months	Increased ICP: Initially → Headache <ul style="list-style-type: none"> <li>• Constant</li> <li>• Progressive</li> <li>• Severe</li> <li>• Worse in morning</li> </ul> As ICP increases: <ul style="list-style-type: none"> <li>• Blurry vision</li> <li>• Projectile vomiting</li> </ul> Severely raised ICP: <ul style="list-style-type: none"> <li>• Cushing's reflex               <ul style="list-style-type: none"> <li>• Bradycardia</li> <li>• Hypertension</li> </ul> </li> </ul>

**Table 2. Consequences of Common Brain Lesions**

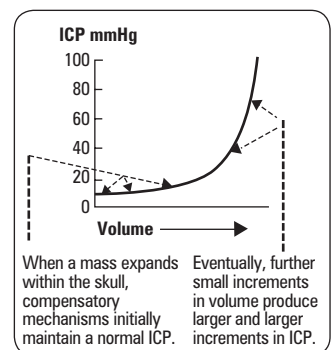
Location of lesion	Consequence
Frontal lobe	<ol style="list-style-type: none"> <li>1. Disinhibition</li> <li>2. Concentration deficits</li> <li>3. Orientation deficits</li> <li>4. Judgement deficits</li> <li>5. <math>\pm</math> Primitive reflex re-emergence</li> </ol>
Right parietal lobe	Spatial neglect syndrome • Contralateral agnosia
Basal ganglia	<ol style="list-style-type: none"> <li>1. Rest tremor</li> <li>2. Chorea</li> <li>3. Athetosis</li> </ol>
Subthalamic nucleus	Contralateral hemiballismus
Amygdala (bilateral)	Kluver-Bucy syndrome* <ol style="list-style-type: none"> <li>1. Hyperorality</li> <li>2. Hypersexuality</li> <li>3. Disinhibition</li> </ol>
Mammillary bodies (bilateral)	Wernicke-Korsakoff syndrome <ol style="list-style-type: none"> <li>1. Wernicke               <ul style="list-style-type: none"> <li>• Confusion</li> <li>• Ophthalmoplegia</li> <li>• Ataxia</li> </ul> </li> <li>2. Korsakoff               <ul style="list-style-type: none"> <li>• Memory loss</li> <li>• Confabulation</li> <li>• Personality changes</li> </ul> </li> </ol>
Hippocampus	Anterograde amnesia
Reticular activating system (midbrain)	Reduced levels of arousal and wakefulness
PPRF	Eyes look away from lesion
Frontal eye fields	Eyes look toward lesion
Cerebellar hemisphere	<ol style="list-style-type: none"> <li>1. Intention tremor</li> <li>2. Limb ataxia</li> <li>3. Fall towards side of lesion</li> </ol>
Cerebellar vermis	<ol style="list-style-type: none"> <li>1. Truncal ataxia</li> <li>2. Dysarthria</li> </ol>

## ICP/Volume Relationship

- adult skull is rigid with a constant intracranial volume
- contents (CSF, blood, brain) are incompressible
- increase in one constituent/space-occupying lesion = increase in ICP
- however, ICP does not rise initially due to compensatory mechanisms (autoregulation):
  - **immediate:** displacement of CSF to lumbar theca, displacement of blood from venous sinuses
  - **delayed:** displacement of ECF or ICF; displacement of brain tissue into compartments under less pressure (herniation)
- once compensation is exhausted, ICP rises exponentially

## Cerebral Blood Flow (CBF)

- CBF depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR)
- normal CPP >50 mmHg in adults
- cerebral autoregulation maintains constant CBF by compensating for changes in CPP, unless:
  - high ICP such that CPP <60 mmHg
  - MAP >150 mmHg or MAP <50 mmHg
  - brain injury: e.g. SAH, severe trauma

**Figure 5. ICP-volume curve**

Adapted from Lindsay KW. Bone I: Neurology and neurosurgery illustrated. © 2004. With permission from Elsevier.



$$\text{CBF} = \text{CPP} / \text{CVR}$$

$$\text{CPP} = \text{MAP} - \text{ICP}$$

## ICP Measurement

- normal ICP <15 mmHg (8-18 cm H<sub>2</sub>O) for adult, 3-7 mmHg (4-9.5 cm H<sub>2</sub>O) for child; varies with patient position
  - moderate elevation: increase in mean pressure >20 mmHg
  - severe elevation: increase in mean pressure >40 mmHg
- waveform: comprised of respiratory and cardiac pulsations (Traube-Hering waves); the amplitude increases with ICP
  - $\beta$ -waves: coarse, variably increased amplitude, frequency 1/2-2/min, often related to respiration
  - plateau waves: elevation of ICP over 50 mmHg lasting 5-20 min, precursor of further deterioration

### Acute Monitoring

- lumbar puncture (LP) (see sidebar)
- intraventricular catheter/ventriculostomy/external ventricular drain (EVD) ("gold standard", also permits therapeutic drainage of CSF to decrease ICP)

### Chronic Monitoring

- fibre optic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

## Elevated ICP

### Etiology

- intracranial space-occupying lesion:
  - tumour
  - pus
  - blood [trauma → hematoma (most common), subarachnoid hemorrhage]
  - depressed skull fracture
  - foreign body
- increased intracranial blood volume
  - vasodilatation (increased pCO<sub>2</sub>/decreased pO<sub>2</sub>/decreased extracellular pH, e.g. hypoventilation)
  - venous outflow obstruction (venous sinus thrombosis, superior vena cava syndrome, space occupying lesion)
  - cranial dependency
- cerebral edema
  - vasogenic (vessel damage, e.g. hypertensive encephalopathy, tumour)
  - cytotoxic (tissue/cell death, e.g. hypoxia, brain injury)
  - osmotic (acute hyponatremia, hepatic encephalopathy)
- impaired autoregulation (hypotension, hypertension, brain injury)
- hydrocephalus (obstructive, non-obstructive)
- tension pneumocephalus (gas within the cranial cavity)
- pseudotumour cerebri (idiopathic intracranial hypertension)
- status epilepticus (chronic seizure resulting in brain edema)

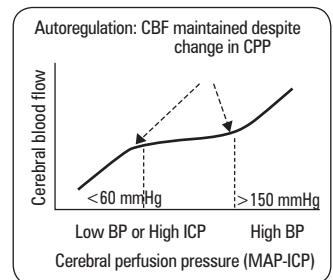
### Clinical Features

#### 1. Acute Elevated ICP

- headache (H/A): worse in the morning, aggravated by stooping and bending
- nausea and vomiting (N/V)
- decreased level of consciousness (LOC) if ICP = diastolic BP, or midbrain compressed
- drop in GCS = best index to monitor progress and predict outcome of acute intracranial process (see *Neurotrauma*, NS30)
- papilledema ± retinal hemorrhages (may take 24-48 h to develop)
- abnormal extra-ocular movements (EOM):
  - CN VI palsy: often falsely localizing (causative mass may be remote from nerve)
  - upward gaze palsy (especially in children with obstructive hydrocephalus)
- herniation syndromes (see *Herniation Syndromes*, NS7)
- focal signs/symptoms due to lesion

#### 2. Chronic Elevated ICP

- H/A
  - postural: worsened by coughing, straining, bending over
  - morning/evening H/A → vasodilatation due to increased CO<sub>2</sub> with recumbency



**Figure 6. Cerebral autoregulation curve**

Adapted from Lindsay, et al. *Neurology and neurosurgery* illustrated. ©2004. With permission from Elsevier



#### Consider Monitoring of ICP in the Following Situations

- Patients with an abnormal head CT and GCS score of 3-8 after cardiopulmonary resuscitation
- Or
- Patients with a normal head CT and GCS score of 3 to 8 AND the presence of two or more of the following:
  - Age over 40 yr
  - Unilateral or bilateral motor posturing
  - Systolic blood pressure less than 90 mmHg
- Postoperative monitoring
- Investigation of normal pressure hydrocephalus (NPH)



Lumbar puncture is contraindicated with known/suspected intracranial mass.



#### Blood Brain Barrier

Glucose and amino acids cross slowly  
Non-polar/lipids cross fast



#### Blood Brain Barrier

Infarction/neoplasm → destroy tight junctions → vasogenic edema



#### Cushing's Triad of Acute Raised ICP (full triad seen in 1/3 of cases)

- Hypertension
- Bradycardia (late finding)
- Irregular respiratory pattern



#### Papilledema

- Elevated optic disc with blurred margins
- Larger blind spot



- visual changes
  - due to papilledema
  - enlarged blind spot, if advanced → episodic constrictions of visual fields (“grey-outs”)
  - optic atrophy/blindness
  - differentiate from papillitis (usually unilateral with decreased visual acuity)
- decreased level of consciousness

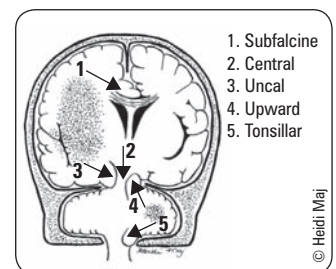
### Investigations

- patients with suspected elevated ICP require an urgent CT/MRI
- ICP monitoring where appropriate

## Herniation Syndromes

**Table 3. Herniation Syndromes**

Herniation Syndrome	Definition	Etiology	Clinical Features
<b>1. Subfalcine</b>	Cingulate gyrus herniates under falx	<ul style="list-style-type: none"> <li>• Lateral supratentorial lesion</li> </ul>	<ul style="list-style-type: none"> <li>• Usually asymptomatic</li> <li>• Warns of impending transtentorial herniation</li> <li>• Risk of ACA compression</li> </ul>
<b>2. Central Tentorial (Axial)</b>	Displacement of diencephalon through tentorial notch	<ul style="list-style-type: none"> <li>• Supratentorial midline lesion</li> <li>• Diffuse cerebral swelling</li> <li>• Late uncal herniation</li> </ul>	<ul style="list-style-type: none"> <li>• Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla</li> <li>• Decreased LOC (midbrain compression) EOM/upward gaze impairment (“sunset eyes”): compression of pretectum and superior colliculi</li> <li>• Brainstem hemorrhage (“Duret’s” – secondary to shearing of basilar artery perforating vessels)</li> <li>• Diabetes insipidus (traction on pituitary stalk and hypothalamus), end-stage sign</li> </ul>
<b>3. Lateral Tentorial (Uncal)</b>	Uncus of temporal lobe herniates down through tentorial notch	<ul style="list-style-type: none"> <li>• Lateral supratentorial lesion (often rapidly expanding traumatic hematoma)</li> </ul>	<ul style="list-style-type: none"> <li>• Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) + ipsilateral EOM paralysis, ptosis (CN III compression)</li> <li>• Decreased LOC (midbrain compression)</li> <li>• Contralateral hemiplegia ± extensor (upgoing) plantar response ± ipsilateral hemiplegia (“Kernohan’s notch” – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle)</li> </ul>
<b>4. Upward</b>	Cerebellar vermis herniates through tentorial incisura	<ul style="list-style-type: none"> <li>• Large posterior fossa mass (common after VP shunting)</li> </ul>	<ul style="list-style-type: none"> <li>• Cerebellar infarct [superior cerebellar artery (SCA) compression]</li> <li>• Hydrocephalus (cerebral aqueduct compression)</li> </ul>
<b>5. Tonsillar</b>	Cerebellar tonsils herniate through foramen magnum	<ul style="list-style-type: none"> <li>• Infratentorial lesion</li> <li>• Following central tentorial herniation</li> <li>• Following LP in presence of intracranial mass lesion</li> </ul>	<ul style="list-style-type: none"> <li>• Neck stiffness and head tilt (tonsillar impaction)</li> <li>• Decreased LOC (midbrain compression)</li> <li>• Flaccid paralysis</li> <li>• Respiratory irregularities, respiratory arrest (compression of medullary respiratory centres)</li> <li>• Blood pressure instability (compression of medullary cardiovascular centres)</li> </ul>



**Figure 7. Herniation types – see Table 4 for description**

## Treatment of Elevated ICP

- CT or MRI to identify etiology, assess for midline shift/herniation
- treat primary cause (i.e. remove mass lesions, ensure adequate ventilation)
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
- goals: keep ICP <20 mmHg, CPP >65 mmHg, MAP >90 mmHg

### Conservative Measures

- elevate head of bed at 30°, maintain neck in neutral position → increases intracranial venous outflow with minimal effect on arterial pressure
- prevent hypotension with fluid and vasopressors, dopamine, norepinephrine prn
- ventilate to normocarbica (pCO<sub>2</sub> 35-40 mmHg) → prevents vasodilatation
- oxygen to maintain pO<sub>2</sub> >60 mmHg → prevents hypoxic brain injury
- osmolar diuresis (mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolality of 315-320)
  - can give rapidly, acts in 15-30 min, must maintain sBP >90 mmHg
- corticosteroids → decrease edema over subsequent days around brain tumour, abscess, blood
  - no proven value in head injury or stroke



### Treatment of Elevated ICP:

#### ICP HEAD

Intubate  
Calm (sedate)/Coma  
Place drain/Paralysis

Hyperventilate  
Elevate head  
Adequate BP  
Diuretic (mannitol)

### Aggressive Measures

- sedation ("light" e.g. barbiturates/codeine → "heavy" e.g. fentanyl/MgSO<sub>4</sub>)
- paralysis with vecuronium → reduces sympathetic tone, reduces HTN induced by muscle contraction
- hyperventilate to pCO<sub>2</sub> 30-35 mmHg
  - use for brief periods only – also results in decreased cerebral blood flow
- drain 3-5 mL CSF via ventricles, assess each situation independently
- insert EVD (if acute) or shunt
- barbiturate-induced coma induced with pentobarbital to reduce cerebral blood flow and metabolism (10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion)
  - decreases mortality, but no improvement in neurological outcome
- decompressive craniectomy is a last resort
- no role for the use of hypothermia in head injury

## Hydrocephalus

- hydrocephalus in children, see *Pediatric Neurosurgery*, NS36

### Definition

- increased CSF volume

### Etiology

- obstruction to CSF flow
- decreased CSF absorption
- increased CSF production (rarely) – e.g. choroid plexus papilloma (0.4-1% of intracranial tumours)

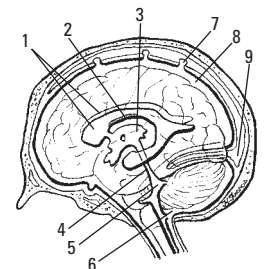
### Epidemiology

- estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1000 live births

### Classification

**Table 4. Classification of Hydrocephalus**

Disorder	Definition	Etiology	Findings on CT/MRI
<b>Obstructive (Non-Communicating) Hydrocephalus</b>	Circulation blocked within ventricular system proximal to the arachnoid granulations	<b>Acquired</b> <ul style="list-style-type: none"> <li>• Aque ductal stenosis (adhesions following infection, hemorrhage)</li> <li>• Intraventricular lesions (tumours e.g. 3rd ventricle colloid cyst, hematoma)</li> <li>• Mass causing tentorial herniation, aqueduct/4th ventricle compression</li> <li>• Others: neurosarcoidosis, abscess/granulomas, arachnoid cysts</li> </ul> <b>Congenital</b> <ul style="list-style-type: none"> <li>• Aque ductal stenosis, Dandy-Walker malformation, Chiari malformation (see <i>Pediatric Neurosurgery</i>, NS37)</li> </ul>	<ul style="list-style-type: none"> <li>• Ventricular enlargement proximal to block</li> <li>• Periventricular hypodensity (transependymal migration of CSF forced into extracellular space)</li> <li>• Sulcal effacement</li> </ul>
<b>Non-Obstructive (Communicating) Hydrocephalus</b>	CSF absorption blocked at extraventricular site = arachnoid granulations	<ul style="list-style-type: none"> <li>• Post-infectious (#1 cause) meningitis, cysticercosis</li> <li>• Post-hemorrhagic (#2 cause) → SAH, IVH, traumatic</li> <li>• Choroid plexus papilloma (rare, causes increased CSF production)</li> <li>• Idiopathic → normal pressure hydrocephalus</li> </ul>	<ul style="list-style-type: none"> <li>• All ventricles dilated</li> </ul>
<b>Normal Pressure Hydrocephalus (NPH)</b>	Persistent ventricular dilatation in the context of normal CSF pressure	<ul style="list-style-type: none"> <li>• Idiopathic (50%)</li> <li>• Others: subarachnoid hemorrhage, meningitis, trauma, radiation-induced</li> </ul>	<ul style="list-style-type: none"> <li>• Enlarged ventricles without increased prominence of cerebral sulci</li> </ul>
<b>Hydrocephalus Ex Vacuo</b>	Ventricular enlargement resulting from atrophy of surrounding brain tissue	<ul style="list-style-type: none"> <li>• Normal aging</li> <li>• Alzheimer's, Creutzfeldt-Jacob Disease</li> </ul>	<ul style="list-style-type: none"> <li>• Enlarged ventricles and sulci</li> <li>• Cerebral atrophy</li> </ul>



1. Lateral ventricles
2. Choroid plexus
3. Third ventricle
4. Cerebral aqueduct (of Sylvius)
5. Fourth ventricle
6. Foramina of Luschka and Magendie
7. Arachnoid granulations
8. Subarachnoid space
9. Superior sagittal sinus

© Karl Francis 2004

**Figure 8. The flow of CSF**



CSF produced by choroid plexus, flows to: ventricles → foramina of Luschka (lateral) and Magendie (medial) → subarachnoid space → absorbed by arachnoid villi/granulations into venous sinuses.

CSF production = CSF reabsorption = ~500 mL/d in normal adults  
 Normal CSF volume ~150 mL (50% spinal, 50% intracranial → 25 mL intraventricular, 50 mL subarachnoid)

### Clinical Features

- acute hydrocephalus
  - signs and symptoms of acute elevated ICP (see *Elevated ICP*, NS6)
  - impaired upward gaze (“sunset eyes”) and/or CN VI palsy
- chronic/gradual onset hydrocephalus (i.e. NPH)
  - gradual onset of classic triad developing over weeks or months
    - ♦ pressure of ventricle on LE motor fibres → gait disturbance (ataxia and apraxia usually initial symptoms)
    - ♦ pressure on cortical bowel/bladder centre → urinary incontinence
    - ♦ pressure on frontal lobes → dementia
  - CSF pressure can be measured within clinically “normal” range



#### Classic Triad of NPH Progression

##### AID

Ataxia/Apraxia of gait  
Incontinence  
Dementia

### Investigations

- CT/MRI (periventricular lucency suggests raised CSF pressure)
- ultrasound (through anterior fontanelle in infants)
- ICP monitoring (e.g. LP) may be used to investigate NPH, test response to shunting (lumbar tap test)
- radionuclide cisternography can test CSF flow and absorption rate (unreliable)
- $\beta$ -2 transferrin assay to test for the presence of CSF leak

### Treatment

- ventricular drainage
- surgical removal of obstruction (if possible) or excision of choroid plexus papilloma
- shunts
  - ventriculoperitoneal (VP): most common
  - ventriculopleural
  - ventriculo-atrial (VA): relatively increased risk of infections, shunt emboli
  - lumboperitoneal: for communicating hydrocephalus and pseudotumour cerebri
- third ventriculostomy (for obstructive hydrocephalus) via ventriculoscopy
- LPs for transient hydrocephalus (e.g. SAH), IVH in premature infants, etc.

### Shunt Complications

Table 5. Shunt Complications

Complication	Etiology	Clinical Features	Investigations
<b>Obstruction</b> (most common)	<ul style="list-style-type: none"> <li>• Obstruction by choroid plexus</li> <li>• Buildup of proteinaceous accretions, blood, cells (inflammatory or tumour)</li> <li>• Infection</li> <li>• Disconnection or damage</li> </ul>	<ul style="list-style-type: none"> <li>• Acute hydrocephalus</li> <li>• Increased ICP</li> </ul>	<ul style="list-style-type: none"> <li>• “Shunt series” (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration)</li> <li>• CT</li> <li>• Radionuclide “shuntogram”</li> </ul>
<b>Infection</b> (3-6%)	<ul style="list-style-type: none"> <li>• <i>S. epidermidis</i></li> <li>• <i>S. aureus</i></li> <li>• <i>P. acnes</i></li> <li>• Gram-negative bacilli</li> </ul>	<ul style="list-style-type: none"> <li>• Fever, N/V, anorexia, irritability</li> <li>• Meningitis</li> <li>• Peritonitis</li> <li>• Signs and symptoms of shunt obstruction</li> <li>• Shunt nephritis (VA shunt)</li> </ul>	<ul style="list-style-type: none"> <li>• CBC</li> <li>• Blood culture</li> <li>• Tap shunt for C&amp;S (LP usually NOT recommended)</li> </ul>
<b>Overshunting</b> (10% over 6.5 yr)	<ul style="list-style-type: none"> <li>• Slit ventricle syndrome, collapse of ventricles leading to occlusion of shunt ports by ependymal lining</li> <li>• Subdural hematoma</li> <li>• Collapsing brain tears bridging veins (especially common in NPH patients)</li> <li>• Secondary craniostylosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic or recurring headaches often relieved when lying down</li> <li>• Asymptomatic</li> <li>• Headaches, vomiting, somnolence</li> <li>• Abnormal head shape</li> </ul>	<ul style="list-style-type: none"> <li>• CT/MRI</li> <li>• Slit-like ventricles on imaging</li> <li>• CT</li> <li>• Clinical</li> <li>• CT</li> </ul>
<b>Seizures</b> (5.5% risk in 1st yr, 1.1% after 3rd yr)			<ul style="list-style-type: none"> <li>• EEG</li> </ul>
<b>Inguinal Hernia</b> (17% incidence with VP shunt inserted in infancy) $\pm$ skin breakdown over hardware	<ul style="list-style-type: none"> <li>• Increased intraperitoneal pressure/fluid results in hernia becoming apparent</li> </ul>	<ul style="list-style-type: none"> <li>• Inguinal swelling, discomfort</li> </ul>	<ul style="list-style-type: none"> <li>• U/S</li> </ul>

## Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)



### Definition

- raised intracranial pressure and papilledema without evidence of any mass lesion, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)

### Etiology

- unknown (majority), but associated with:
  - lateral venous sinus thrombosis
  - habitus/diet: obesity, hyper/hypovitaminosis A
  - endocrine: reproductive age, menstrual irregularities, Addison's/Cushing's disease, thyroid irregularities
  - hematological: iron deficiency anemia, polycythemia vera
  - drugs: steroid administration or withdrawal, tetracycline, nalidixic acid, etc.
- risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones ("fat, female, fertile, forties")

### Epidemiology

- incidence ~0.5/100,000 per year
- usually in 3rd and 4th decade (F>M)

### Clinical Features

- symptoms and signs of raised ICP (H/A in >90%, pulsatile intracranial noise), but no LOC or diplopia
- decreased visual acuity, papilledema, visual field defect, optic atrophy (key morbidity)
- usually self-limited, recurrence is common, chronic in some patients
- risk of blindness is not reliably correlated to symptoms or clinical course

### Investigations

- CT: normal
- CSF studies: normal
- MRI: must look for venous sinus thrombosis

### Treatment

- rule out conditions that cause intracranial hypertension (especially sinus thrombosis)
- discontinue offending medications, encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic or furosemide
- if above fail: serial LPs, shunt
- optic nerve sheath decompression (if progressive impairment of visual acuity)
- 2-yr follow-up with imaging to rule out occult tumour, ophthalmology follow-up



#### Important Features to Note on CT and MRI (± contrast enhancement)

- Lesions (± edema, necrosis, hemorrhage)
- Midline shifts and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)

## Tumours

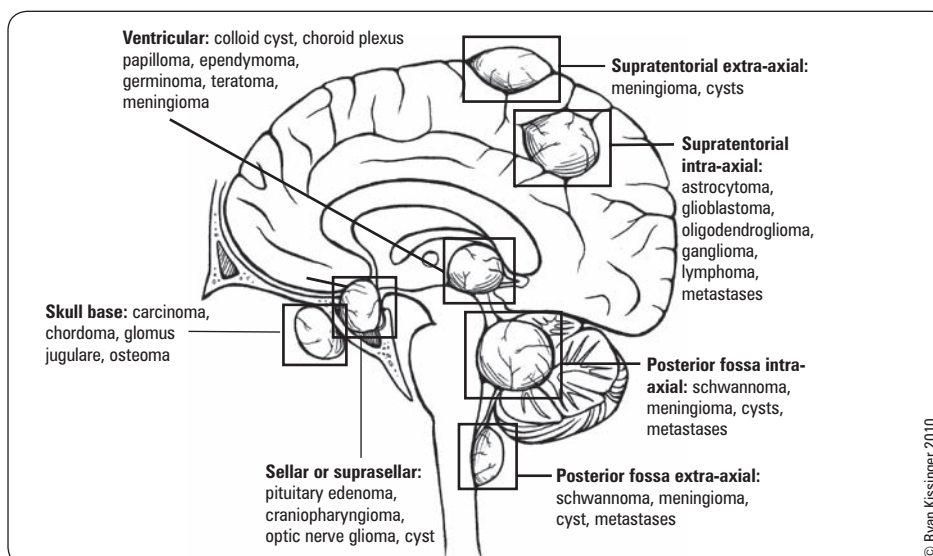


Figure 9. Tumours



#### DDx for Ring Enhancing Lesion on CT with Contrast

##### MAGICAL DR

- Metastases\*
- Abscess\*
- Glioblastoma (high grade astrocytoma)\*
- Infarct
- Contusion
- AIDS (toxoplasmosis)
- Lymphoma
- Demyelination
- Resolving hematoma
- (\* 3 most common Dx's)



#### Primary Sources of Metastatic Brain Tumours

Lung	44%
Breast	10%
Kidney (RCC)	7%
GI	6%
Melanoma	3%

### Classification

- primary vs. metastatic, intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, devastating due to expansion of mass in fixed volume of skull (mass effect)
- malignant: implies rapid growth, invasiveness, but rarely extracranial metastasis
- types of intracranial tumours (\* = most common)
  - neuroepithelial tissue
    - ♦ astrocytic tumours: astrocytoma, glioblastoma
    - ♦ oligodendroglial tumours
    - ♦ oligoastrocytic tumours
    - ♦ neuronal and mixed neuronal-glial tumours: ganglion cell tumours, cerebral neurocytomas/neuroblastomas
    - ♦ embryonal tumours: medulloblastoma, neuroectodermal
    - ♦ other: pineal, ependymal, and choroid plexus tumours
  - meningeal: meningiomas\*, mesenchymal, hemangioblastomas
  - cranial and paraspinal nerves: schwannoma, neurofibroma
  - lymphomas and hematopoietic neoplasms
  - germ cell: germinomas, teratomas
  - pituitary adenomas\*
  - sellar region: craniopharyngiomas, spindle cell oncocyoma
  - cysts: epidermoid/dermoid cysts, colloid cysts
  - local extension: chordomas, glomus jugulare tumours
  - metastatic tumours

### Clinical Features

- progressive neurological deficit (70%): usually motor weakness,  $\pm$  CN deficits, sensory, cognitive, personality, endocrine deficits (these may localize lesion)
- H/A (50%)  $\pm$  symptoms of elevated ICP (see *Elevated ICP*, NS6)
- N/V (40%)
- seizures (25%)
- papilledema, vision changes
- symptoms suggestive of TIA (ictal, post-ictal, or ischemic 2° to “steal phenomenon”)
- rarely presents with hemorrhage
- familial syndromes associated with CNS tumours
  - von Hippel-Lindau (hemangioma)
  - tuberous sclerosis (astrocytoma)
  - neurofibromatosis type 1 and 2 (astrocytoma, acoustic neuroma respectively)
  - Li-Fraumeni (astrocytoma)
  - Turcot syndrome (glioblastoma multiforme)
  - multiple endocrine neoplasia type 1 (MEN-1) (pituitary adenoma)

### Investigations

- CT, MRI, stereotactic biopsy (tissue diagnosis), metastatic work-up

### Treatment

- conservative: serial Hx, Px, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce cytotoxic cerebral edema, pharmacological (see *Pituitary Adenoma*, NS14)
- surgical: total or partial excision (decompressive, palliative), shunt if hydrocephalus
- radiotherapy: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (e.g. Gamma Knife®)
- chemotherapy: e.g. alkylating agents (temozolomide)

**Table 6. Tumour Types: Age, Location**

Age	Supratentorial	Infratentorial (posterior fossa)
<15 yr	Astrocytoma (all grades) (50%) Craniopharyngioma (2-5%) Others: pineal region tumours, choroid plexus tumours, ganglioglioma, DNET	Medulloblastoma (15-20%) Cerebellar astrocytoma (15%) Ependymoma (9%) Brainstem astrocytoma
>15 yr	High grade astrocytoma (12-15%, e.g. GBM) Metastasis (15-30%, includes infratentorial) Meningioma (15-20%) Low grade astrocytoma (8%) Pituitary adenoma (5-8%) Oligodendroglioma (5%) Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts	Metastasis Acoustic neuroma (schwannoma) (5-10%) Hemangioblastoma (2%) Meningioma



#### Management of Single Brain Metastasis: A Practice Guideline

*Curr Oncol* 2007;14:131-143

**Background:** In Ontario the benefits of surgical resection  $\pm$  adjuvant whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) in confirmed single brain metastasis are summarized in this manuscript.

**Methods:** Medline, Cancerlit, Embase and Cochrane Library databases as well as abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2005) and American Society for Therapeutic Radiology and Oncology (1998-2004) were systematically searched for relevant evidence. Outcomes were compared in terms of survival, local control of disease, quality of life, and adverse effects. The finalized review of these works was condensed into a practice guideline approved by the Neuro-oncology DSG and Ontario practitioners (through an electronic survey).

**Results:** Two of three RCTs reported a significant survival benefit for patients with single brain metastasis who underwent surgical resection as compared with those who received WBRT alone. The RCT that compared surgical resection plus WBRT with surgical resection alone reported no significant difference in overall survival or length of functional independence; however, tumour recurrence at the site of the metastasis and anywhere in the brain was less frequent in patients who received WBRT as compared with patients in the observation group. In addition, patients who received WBRT were less likely to die from neurologic causes. Results of the RCT that compared WBRT and SRS with WBRT alone indicated a significant improvement in median survival in patients who received SRS.

**Conclusions:** Surgical excision should be considered for patients with good performance status, minimal or no evidence of extracranial disease, and a surgically accessible single brain metastasis amenable to complete excision. Furthermore, to reduce the risk of tumour recurrence postoperative WBRT should be considered. As an alternative to surgical resection, WBRT followed by SRS boost should be considered, however, the evidence is insufficient to recommend SRS alone as a single-modality therapy.



Primary CNS lymphoma reported in 6-20% of HIV infected patients.



#### Brain Metastasis

~1/3 of all adult brain tumours  
Well circumscribed, often at grey-white matter junction



#### Primary Brain Tumours

- Rarely undergo metastasis
- Adults = mostly supratentorial
- Children = mostly infratentorial

Table 7. Unique Presentations of Brain Tumours

Tumour	Features	Diagnosis	Notes
<b>Tumours at the base of the frontal lobe</b>	Foster-Kennedy Syndrome 1. Inappropriate behaviour 2. Ipsilateral optic nerve atrophy 3. Contralateral papilledema 4. Anosmia	CT MRI (better)	
<b>Craniopharyngioma</b>	1. Youngsters 2. Short for age 3. Bitemporal hemianopsia	1. X-ray: calcified lesion above sella 2. MRI	
<b>Prolactinomas</b>	1. Young women 2. Amenorrhea 3. Galactorrhea	1. $\beta$ -hCG $\rightarrow$ r/o pregnancy 2. TSH, $T_4 \rightarrow$ r/o hypothyroidism 3. Prolactin level 4. MRI	Treat with 1. Bromocriptine/cabergoline 2. Surgery if non-responsive to bromocriptine or wants to get pregnant
<b>Acromegaly</b>	1. Enlarged hands, feet, tongue 2. HTN 3. DM 4. Sweaty hands 5. Headache 6. History of wedding bands/hats not fitting anymore	1. Somatomedin C level 2. MRI	Treat with 1. Radiation, or 2. Surgery (better)
<b>Pituitary apoplexy</b>	Bleed into tumour $\rightarrow$ destroy pituitary gland 1. Pituitary tumour • Headache • Visual loss • Endocrine issues 2. Episodic severe headaches 3. Increased compression of nearby structures • Decreased visual acuity • Bilateral pallor of optic nerves 4. Pituitary destruction • Stupor • Hypotension	1. CT 2. MRI (better)	Must 1. Replace steroid hormones 2. Eventually replace other hormones
<b>Pineal gland tumour</b>	1. Loss of upper gaze 2. "Sunset eyes" (Parinaud syndrome)	1. CT 2. MRI (better)	
<b>Brain tumours in children</b>	Often posterior fossa tumours 1. Cerebellar symptoms • Stumbling • Truncal ataxia 2. "Knee-chest" position to relieve headache	1. CT 2. MRI (better)	
<b>Brain abscess</b>	Similar symptoms as brain tumours + fever + nearby infection	1. CT	

## Metastatic Tumours

- most common brain tumour seen clinically
- 15-30% of cancer patients present with cerebral metastatic tumours
  - most common sources : lungs, breast
  - other sources : kidney, thyroid, stomach, prostate, testis, melanoma
- hematogenous spread most common

### Location

- 80% are hemispheric, often at grey-white matter junction or junction of temporal-parietal-occipital lobes (likely emboli spreading to terminal MCA branches)

### Investigations

- identify primary tumour
  - metastatic work-up (CXR, CT chest/abdo, abdominal U/S, bone scan, mammogram)
- CT with contrast  $\rightarrow$  round, well-circumscribed, often ring enhancing, ++ edema, often multiple
- MRI more sensitive, especially for posterior fossa
- consider biopsy in unusual cases, or if no primary identified

### Treatment

- medical
  - phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  - dexamethasone to reduce edema given with ranitidine
  - chemotherapy (e.g. small cell lung cancer)

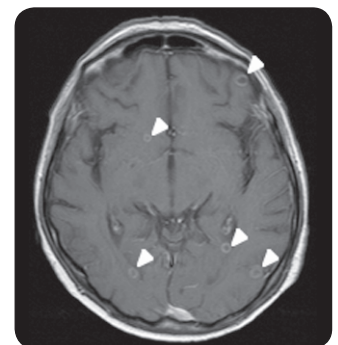


Figure 10. Multiple brain metastases (see arrows)



- radiation
  - stereotactic radiosurgery: for discrete, deep-seated/inoperable tumours
  - multiple lesions: use whole brain radiation therapy (WBRT); consider stereotactic radiosurgery if <3 lesions
  - post-op WBRT is commonly used
- surgical
  - single/solitary lesions: use surgery + radiation

### Prognosis

- median survival without treatment once symptomatic is ~1 mo, with optimal treatment 6-9 mo but varies depending on primary tumour type

## Astrocytoma

- most common primary intra-axial brain tumour, common in 4-6th decades

**Table 8. Astrocytoma Grading System**

World Health Organization (WHO)	Typical CT/MRI Findings	Survival
I – Pilocytic astrocytoma	± mass effect, ± enhancement	>10 yr, cure if gross total resection
II – Low grade/diffuse	Mass effect, no enhancement	5 yr
III – Anaplastic	Complex enhancement	1.5-2 yr
IV – Glioblastoma multiforme (GBM)	Necrosis (ring enhancement)	12 mo, 10% at 2 yr

### Clinical Features

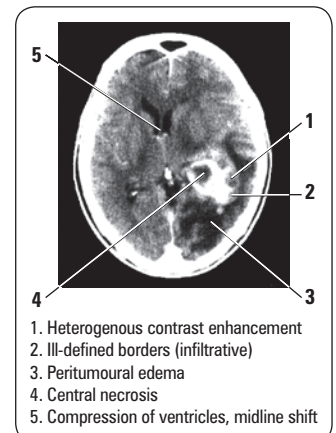
- sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
- symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

### Investigations

- CT/MRI with contrast: variable appearance depending on grade (see Table 8)
- tissue biopsy: WHO grade and histology correlates with prognosis, but 25% chance of sampling error due to tumour heterogeneity

### Treatment

- low grade diffuse astrocytoma
  - close follow-up, radiation, chemotherapy, surgery all valid options
  - surgery: not curative, trend towards better outcomes
  - radiotherapy alone or post-op prolongs survival (retrospective evidence)
  - chemotherapy: usually reserved for tumour progression
- high grade astrocytomas (anaplastic astrocytoma and GBM)
  - surgery
    - ♦ gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant temozolomide
      - except: extensive dominant lobe GBM, significant bilateral involvement, end of life near, extensive brainstem involvement
    - ♦ stereotactic biopsy if resection not possible, followed by fractionated radiation with 2 cm margin
  - expectant (based on functional impairment – Karnofsky score <70; patient's/family's wishes)
  - aim to prolong "quality" survival
  - chemotherapy: ~20% response rate, temozolomide (agent of choice); better response to temozolomide predicted by MGMT gene hypermethylation
- multiple gliomas: WBRT ± chemotherapy



**Figure 11. High grade astrocytoma on CT**



### Karnofsky General Cancer Performance Status Scale Rating Criteria

Rating Criteria (%)	
100	No complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospital admission is indicated although death not imminent
20	Very sick; hospital admission necessary; active supportive treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead



## Meningioma

- mostly benign (1-2% anaplastic), slow-growing, extra-axial, circumscribed (non-infiltrative), arise from arachnoid membrane
- often calcified, cause hyperostosis of adjacent bone
- classically see Psammoma bodies on histology
- common locations: parasagittal convexity or falx (70%), sphenoid wing, tuberculum sellae, foramen magnum, olfactory groove

### Clinical Features

- middle aged, slight female preponderance (M:F = 2:3), high progesterone receptors (increase in size with pregnancy), symptoms of increased ICP, focal deficits, usually solitary (10% multiple, likely with loss of NF2 gene/22q12 deletion)

### Investigations

- CT with contrast: homogeneous, densely enhancing, along dural border (“dural tail”), well circumscribed (Figure 12)
- contrast enhanced MRI provides better detail
- angiography
  - most are supplied by external carotid feeders (meningeal vessels)
  - also assesses venous sinus involvement, “tumour blush” commonly seen (prolonged contrast image)
- octreotide scintigraphy: to establish if expression of somatostatin receptor

### Treatment

- conservative management for non-progressive, asymptomatic lesions
- surgery is treatment of choice if symptomatic or progression on sequential imaging (curative if complete resection)
- SRS may be an option for lesions <3 cm
- endovascular embolization to facilitate surgery
- SRS or XRT for recurrent atypical/malignant meningiomas

### Prognosis

- >90% 5-yr survival, recurrence rate variable (often ~10-20%)
- depends on extent of resection (Simpson's classification)



#### WHO Classification of Meningioma (by histology)

- Grade 1: low risk of recurrence
- Grade 2: intermediate risk of recurrence
- Grade 3: high risk of recurrence

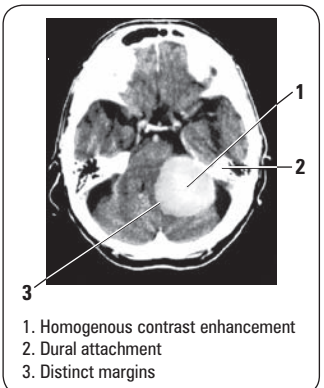


Figure 12. Meningioma on CT



Progressive unilateral or asymmetrical sensorineural hearing loss = acoustic neuroma until proven otherwise.

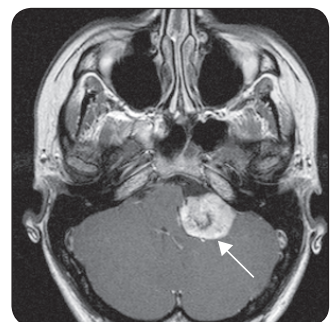


Figure 13. Vestibular schwannoma (tumour in cerebello-pontine angle)



## Vestibular Schwannoma (Acoustic Neuroma)

- slow-growing (average of 1 mm/yr), benign posterior fossa tumour
- arises from vestibular component of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of neurofibromatosis type II
- epidemiology: all age groups affected, peaks at 4<sup>th</sup>-6<sup>th</sup> decades

### Clinical Features

- compression of structures in CPA, often CN VIII (hearing loss 98%, tinnitus, dysequilibrium), followed by CN V and VII
- ataxia and raised ICP are late features

### Investigations

- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/specific), CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

### Treatment

- conservative: serial imaging
- radiation: stereotactic radiosurgery or fractionated radiotherapy
- surgery if: lesion >3 cm, brainstem compression, edema, hydrocephalus
  - curable if complete resection (almost always possible)
  - operative complications: CN VII, VIII dysfunction (only significant disability if bilateral), CSF leak

## Pituitary Adenoma

- primarily from anterior pituitary, 3<sup>rd</sup>-4<sup>th</sup> decades, M=F
- incidence in autopsy studies approximately 20%
- classification
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
- differential: parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid aneurysm

### Clinical Features

- mass effects
  - H/A
  - bitemporal hemianopsia (compression of optic chiasm) (see [Neurology](#), N12 for details of visual field deficit)
  - CN III, IV, V<sub>1</sub>, V<sub>2</sub>, VI palsy (compression of cavernous sinus)

- endocrine effects
  - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
  - ACTH production: Cushing's disease, hyperpigmentation
  - GH production: acromegaly/gigantism
  - panhypopituitarism (hypothyroidism, hypoadrenalism, hypogonadism)
  - associated MEN-1 syndrome
  - diabetes insipidus
- pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
  - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, and panhypopituitarism
  - CSF rhinorrhea and seizures (rare)
  - signs and symptoms of subarachnoid hemorrhage (rare)

### Investigations

- formal visual fields, CN testing
- endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose, FSH/LH, IGF-1), electrolytes, urine electrolytes, and osmolarity
- imaging (MRI with and without contrast)

### Treatment

- medical
  - for apoplexy: rapid corticosteroid administration  $\pm$  surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing's: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide)  $\pm$  bromocriptine
  - endocrine replacement therapy
- surgical
  - trans-sphenoidal, trans-ethmoidal, trans-cranial approaches for non-secreting adenomas causing mass effect and Cushing/acromegaly (50% cure rate)



**Go Look For The Adenoma Please – GH, LH, FSH, TSH, ACTH, Prolactin**  
A compressive adenoma in the pituitary will impair hormone production in this order (i.e. GH-secreting cells are most sensitive to compression).

## Pus



### Sources of Pus/Infection

- four routes of microbial access to CNS
  1. hematogenous spread (most common): arterial and retrograde venous
    - ♦ adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
    - ♦ children: congenital cyanotic heart disease with R to L shunt
    - ♦ immunosuppression (AIDS – toxoplasmosis)
  2. direct implantation (dural disruption)
    - ♦ trauma
    - ♦ iatrogenic (e.g. following LP, post-op)
    - ♦ congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
  4. spread from PNS (e.g. viruses: rabies, herpes zoster)
- common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
    - ♦ treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
    - ♦ treatment: surgical drainage and antibiotics, 20% mortality
  - meningitis, encephalitis (see [Infectious Diseases](#), ID19, ID20)
  - cerebral abscess (see *Cerebral Abscess*, below)

## Cerebral Abscess

### Definition

- pus in brain substance, surrounded by tissue reaction (capsule formation)

### Etiology

- modes of spread (see above): 10-60% of patients have no cause identified
- pathogens
  - *Streptococcus* (most common), often anaerobic or microaerophilic
  - *Staphylococcus* (penetrating injury)
  - Gram-negatives, anaerobes (*Bacteroides*, *Fusobacterium*)
  - in neonates: *Proteus* and *Citrobacter* (exclusively)
  - immunocompromised: fungi and protozoa (*Toxoplasma*, *Nocardia*, *Candida albicans*, *Listeria monocytogenes*, *Mycobacterium* and *Aspergillus*)

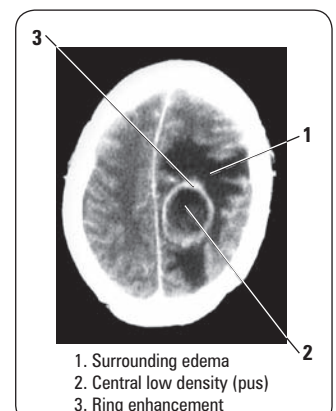


Figure 14. Cerebral abscess on CT

### Risk Factors

- lung abnormalities [infection, AV fistulas; especially Osler-Weber-Rendu syndrome (aka hereditary hemorrhagic telangiectasia)]
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess

### Clinical Features

- focal neurological signs and symptoms
  - H/A, decreased LOC; hemiparesis and seizures in 50%
- mass effect, increased ICP and sequelae (cranial enlargement in children)
- hemiparesis and seizures in 50%
- $\pm$  signs and symptoms of systemic infection (low-grade fever, leukocytosis)

### Complications

- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

### Investigations

- CT scan often first test in emergency department (see Figure 14)
- MRI
  - imaging of choice
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)
- WBC/ESR may be normal, blood cultures rarely helpful and LP contraindicated if large mass
- CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

### Treatment

- aspiration  $\pm$  excision and send for Gram stain, acid fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin (6-8 wk therapy)
  - revise antibiotics when C&S known
- anti-convulsants (1-2 yr)
- follow up CT is critical (do weekly initially, more frequent if condition deteriorates)

### Prognosis

- mortality with appropriate therapy ~10%, permanent deficits in ~50%



#### Brain Abscess in 142 Patients: Factors Influencing Outcome and Mortality *Surg Neurol* 2006;65:557-562

**Introduction:** This study looked to identify prognostic factors for outcome and mortality in patients with brain abscess.

**Methods:** 142 patients (98 male, mean age 41.5 yr, range 2-84) were reviewed retrospectively and had (a) a localized brain parenchymal lesion with ring enhancement by contrast visible on CT or MRI and (b) at least one of: positive blood cultures, positive cultures of intracerebral materials, or histology of the intracerebral lesion suggesting brain abscess. Outcome was assessed according to the Glasgow Outcome Score (GOS). All patients were treated with IV antibiotics for at least 4 wk. Drainage and excision was performed on lesions  $>2.5$  cm in largest diameter.

**Results:** A total of 105 patients had a favourable outcome: 63 (44.4%) had full recovery and 42 (29.6%) had mild deficits. 37 patients had an unfavourable outcome: 24 died in hospital and 13 had moderate to severe disability. Improved outcome was associated with being male (OR 9.81,  $p=0.002$ ), having a presenting GCS  $>12$  (OR 6.20,  $p=0.019$ ), being sepsis-free throughout hospitalization (OR 761.49,  $p<0.001$ ) or having gram-positive cocci grown from abscess culture (OR 42.3,  $p=0.013$ ). No other variables proved to be prognostic.

**Conclusion:** Surgical management (craniotomy drainage, stereotactic aspiration or excision) is recommended in all patients with regards to obtaining culture materials, even when the abscess is small ( $<2.5$  cm), deeply seated or multiple in nature. The improved prognosis associated with being sepsis-free and/or growing gram-positive cocci, likely results in part from having culture and sensitivity analysis to guide appropriate antimicrobial management.

## Blood

**Table 9. Comparison of Epidemiology and Etiology of Intracranial Bleeds**

Types of Hematoma/Hemorrhage	Etiology	Epidemiology	Clinical Features	CT Features	Treatment	Prognosis
<b>Epidural Hematoma</b>	Skull fracture causing middle meningeal bleed	M>F (4:1), associated with trauma	Lucid interval before LOC	Hyperdense lenticular mass with sharp margins, usually limited by suture lines	Craniotomy	Good with prompt management (Note: respiratory arrest can occur from uncal herniation)
<b>Acute SDH</b>	Ruptured subarachnoid bridging vessels	Age $>50$ , associated with trauma	No lucid interval, hemiparesis, pupillary changes	Hyperdense crescentic mass, crossing sutures lines	Craniotomy if bleed $>1$ cm thick	Poor
<b>Chronic SDH</b>	Ruptured subarachnoid bridging vessels	Age $>50$ , EtOH abusers, anti-coagulated	Often asymptomatic, minor H/A, confusion, signs of increased ICP	Hypodense crescentic mass, crossing suture lines	Burr hole to drain; craniotomy if recurs	Good
<b>SAH</b>	Trauma, spontaneous (aneurysms, idiopathic, AVM)	Age 55-60 20% cases under age 45	Sudden onset thunderclap headache, signs of increased ICP	Hyperdense blood in cisterns/fissures (sensitivity decreases over time)	Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed	Poor: 50% mortality 30% of survivors have moderate to severe disability
<b>ICH</b>	HTN, vascular abnormality, tumours, infections, coagulopathy	Age $>55$ , male, drug use (cocaine, EtOH, amphetamine)	TIA-like symptoms, signs of increased ICP	Hyperdense intraparenchymal collection	Medical: decrease BP, control ICP Surgical: craniotomy	Poor: 44% mortality due to cerebral herniation

## Extradural ("Epidural") Hematoma



### Etiology

- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

### Epidemiology

- young adult, male > female = 4:1; rare before age of 2 or after age 60

### Clinical Features

- classic sequence (seen in <30%): post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilatation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, HTN and respiratory distress
- deterioration can take hours to days

### Investigations

- CT without contrast: "lenticular-shaped" usually limited by suture lines (see Figure 15)

### Treatment

- admission, observation with serial CT indicated if all of the following are present:
  - small volume clot, minimal midline shift (MLS <5 mm), GCS >8, no focal deficit
- otherwise, craniotomy to evacuate clot, follow up CT
- mannitol pre-op if elevated ICP/brain herniation

### Prognosis

- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-op
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)

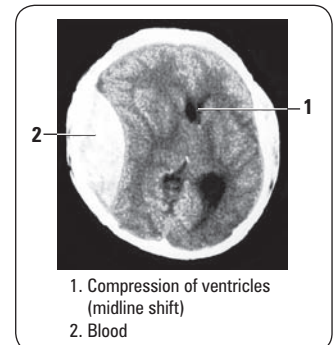


Figure 15. Extradural hematoma on CT



### CT Density and MRI Appearance of Blood

Time	CT	MRI T1	MRI T2
<b>Acute</b> (<72 h)	Hyper.	Grey	Black
<b>Subacute</b> (<3 wk)	Iso.	White	White
<b>Chronic</b> (>3 wk)	Hypo.	Black	Black

MRI-T1: "George Washington Bridge"  
MRI-T2: "Oreo" cookie –  
Black/White/Black

## Subdural Hematoma (SDH)



### ACUTE SUBDURAL HEMATOMA

#### Etiology

- rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration

#### Risk Factors

- trauma, acceleration-deceleration injury, anti-coagulants, alcohol, cerebral atrophy, infant head trauma (see [Pediatrics](#), P86)

#### Clinical Features

- no lucid period, signs and symptoms can include altered LOC, pupillary irregularity, hemiparesis

#### Investigations

- CT: hyperdense concave "crescentic" mass, crossing suture lines (see Figure 16)

#### Treatment

- craniotomy if clinically symptomatic, if hematoma >1 cm thick, or if MLS >5 mm (optimal if surgery <4 h from onset); otherwise observe with serial imaging

#### Prognosis

- poor overall since the brain parenchyma is often injured (mortality range is 50%-90%, due largely to underlying brain injury)
- prognostic factors: initial GCS and neurologic status, post-op ICP

### CHRONIC SUBDURAL HEMATOMA

#### Etiology

- many start out as acute SDH
- blood within the subdural space evokes an inflammatory response:
  - fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot
- course is determined by the balance of rebleeding from neomembranes and resorption of fluid

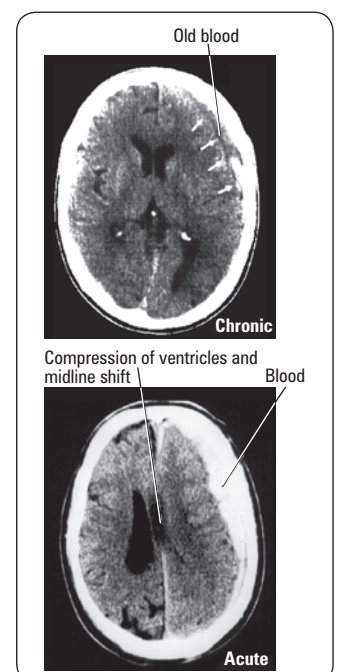


Figure 16. Subdural hematoma on CT



**Risk Factors**

- older, alcoholics, patients with CSF shunts, anti-coagulants, coagulopathies

**Clinical Features**

- often due to minor injuries or no history of injury
- may present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP  $\pm$  seizures, progressive dementia, gait problem
- obtundation disproportionate to focal deficit; “the great imitator” of dementia, tumours

**Investigations**

- CT: hypodense (liquefied clot), crescentic mass (see Figure 16)

**Treatment**

- seizure prophylaxis only if post-traumatic seizure
- reverse coagulopathies
- burr hole drainage of liquefied clot indicated if symptomatic or thickness  $>1$  cm; craniotomy if recurs more than twice

**Prognosis**

- good overall as brain usually undamaged, but may require repeat drainage

## Cerebrovascular Disease

**Ischemic Cerebral Infarction (80%)**

- embolic, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc. (see [Neurology](#), N43)

**Intracranial Hemorrhage (20%)**

- subarachnoid hemorrhage (SAH), spontaneous intracerebral hemorrhage (ICH), intraventricular hemorrhage (IVH)

## Subarachnoid Hemorrhage (SAH)

**Definition**

- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

**Etiology**

- trauma (most common)
- spontaneous
  - ruptured aneurysms (75-80%)
  - idiopathic (14-22%)
  - AVMs (4-5%)
- coagulopathies (iatrogenic or primary), vasculitides, tumours, cerebral artery dissections ( $<5\%$ )

**Epidemiology**

- $\sim 10-28/100,000$  population/yr
- peak age 55-60, 20% of cases occur under age 45

**Risk Factors**

- hypertension
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance abuse (cigarette smoking, cocaine, alcohol)
- conditions associated with high incidence of aneurysms (see *Intracranial Aneurysms*, NS21)

**Clinical Features of Spontaneous SAH**

- sudden onset (seconds) of severe “thunderclap” headache usually following exertion and described as the “worst headache of my life” (up to 97% sensitive, 12-25% specific)
- nausea/vomiting, photophobia
- meningismus (neck pain/stiffness, positive Kernig’s and Brudzinski’s sign)
- decreased LOC (due to either raised ICP, ischemia, seizure)
- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
- reactive hypertension

**Fisher Grade (SAH on CT scan)**

Grade	Finding
1	Normal scan
2	$<1$ mm thick blood
3	$>1$ mm thick blood
4	SAH + ICH or IVH

**Hunt and Hess Grade (clinical grading scale for SAH)**

Grade	Description
1	No Sx or mild H/A and/or mild meningismus
2	Grade 1 + CN palsy
3	Confusion/lethargy, mild hemiparesis or aphasia
4	GCS $<15$ but $>8$ , moderate-severe hemiparesis, mild rigidity
5	Coma (GCS $<9$ ), decerebrate, moribund appearance

Mortality of Grade 1-2 20%, increased with grade



- sentinel bleeds
  - represents undiagnosed SAH
  - SAH-like symptoms lasting <1 d (“thunderclap H/A”)
  - may have blood on CT or LP
  - ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
- differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

### Investigations

- non-contrast CT (Figure 17) – for diagnosis of SAH
  - 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  - may be negative if small bleed or presentation delayed several days
  - acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
- lumbar puncture (highly sensitive) – for diagnosis of SAH if CT negative but high suspicion:
  - elevated opening pressure (>18 cm H<sub>2</sub>O)
  - bloody initially, xanthochromic supernatant with centrifugation (“yellow”) by ~12 h, lasts 2 wk
  - RBC count usually >100,000/mm<sup>3</sup> without significant drop from first to last tube (in contrast to traumatic tap)
  - elevated protein due to blood breakdown products
- four vessel cerebral angiography (“gold standard” for aneurysms)
  - demonstrates source of SAH in 80-85% of cases
  - angiogram negative SAH: repeat angiogram in 7-14 d, if negative → “perimesencephalic SAH”
- MRA and CTA: sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

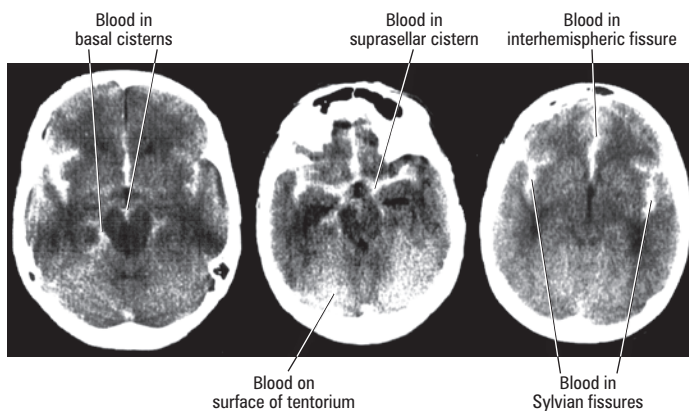


Figure 17. Diagnosis of SAH

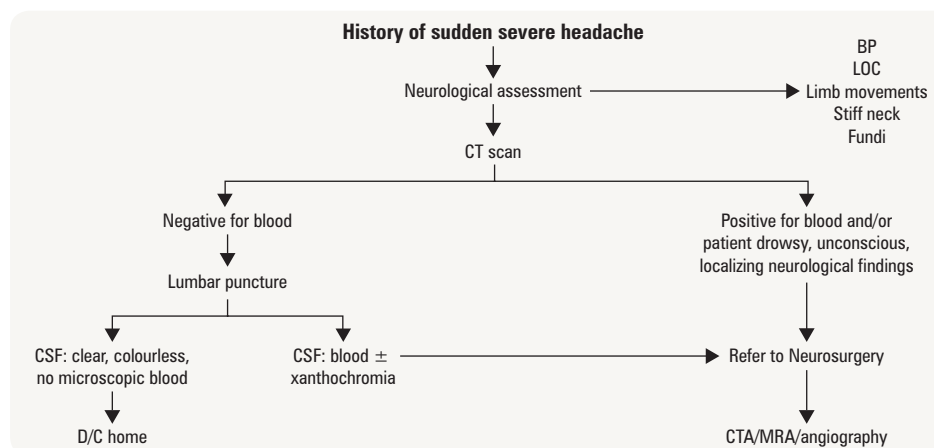


Figure 18. Approach to SAH



### World Federation of Neurological Surgeons Grading of SAH

WFNS Grade	GCS Score	Aphasia, Hemiparesis, or Hemiplegia
0 *		
1	15	–
2	13-14	–
3	13-14	+
4	7-12	+ or –
5	3-6	+ or –

\*Intact aneurysm



### Nontraumatic Subarachnoid Hemorrhage in the Setting of Negative Cranial Computed Tomography Results: External Validation of a Clinical and Imaging Prediction Rule

*Ann Emerg Med* 2012;59:460-8.e1-7. doi:10.1016

**Background:** Two rules for SAH diagnosis exist.

A clinical prediction rule states that patients with acute severe headache but without the clinical variables age ≥40 yr, neck pain, loss of consciousness, or onset of headache with exertion are at low risk for SAH. An imaging prediction rule bases diagnosis on non-contrast cranial CT for patients within 6 h of headache onset.

**Methods:** Matched case-control study of 55 patients at 21 emergency departments between 2000 and 2011, and diagnoses were verified by lumbar puncture.

**Results:** The clinical prediction rule for diagnosis of SAH was 97.1% sensitive, 22.7% specific, and had a negative likelihood ratio of 0.13. Using the imaging prediction rule resulted in a false negative rate of 20%.

**Conclusions:** Performing the clinical and imaging rules together has the potential for maximizing sensitivity of prediction and reducing rates of lumbar puncture, but using imaging alone can result in missed cases.

## Treatment

- admit to ICU or NICU
  - oxygen/ventilation prn
  - NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
  - aim to maintain sBP = 120-150 (balance of vasospasm prophylaxis, risk of re-bleed, risk of hypotension since CBF autoregulation impaired by SAH)
  - cardiac rhythm monitor, Foley prn, strict monitoring of ins and outs
- medications:
  - IV NS with 20 mmol KCl/L at 125-150 cc/h
  - nimodipine 60 mg PO/NG q4h x 21 d for vasospasm neuroprotection; may discontinue earlier if patient is clinically well
  - seizure prophylaxis: levetiracetam (Keppra®) 500 mg PO/IV q12h x 1 wk
  - mild sedation prn

## Complications

- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood
  - onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
  - clinical features (delayed ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor)
  - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
  - “symptomatic” vasospasm in 20-30% of SAH patients
  - “radiographic” vasospasm in 30-70% of arteriograms performed 7 d following SAH
  - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
  - risk of cerebral infarct and death
  - treatment
    - ♦ hyperdynamic (“triple H” – see sidebar) therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
    - ♦ direct vasodilation via angioplasty or intraarterial verapamil for refractory cases
- hydrocephalus (15-20%): due to blood obstructing CSF drainage
  - can be acute or chronic, requires extraventricular drain (EVD) or shunt, respectively
- neurogenic pulmonary edema
- hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECFV loss), not SIADH
- diabetes insipidus
- cardiac: arrhythmia (>50% have ECG changes), MI, CHF

## Prognosis

- 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
- 30% of survivors have moderate to severe disability
- a major cause of mortality is rebleeding, for aneurysms:
  - risk of rebleed: 4% on first day, 15-20% within 2 wk, 50% by 6 mo
  - if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  - only prevention is early clipping or coiling of “cold” aneurysm
  - rebleed risk for “perimesencephalic SAH” is approximately same as for general population



### Calcium Antagonists for Aneurysmal Subarachnoid Hemorrhage

*Cochrane DB Syst Rev* 2007;3:CD0000277

**Introduction:** This study looked to review the evidence in regards as to whether calcium antagonists improve the outcome in patients with aneurysmal subarachnoid hemorrhage.

**Methods/Population:** The review included 3361 patients presenting with aneurysmal subarachnoid hemorrhage from 16 RCTs comparing treatment with calcium antagonists vs. control from 1980 to March 2006.

**Results:** The results were based mainly on one large trial of oral nimodipine, which showed a RR of 0.67 (95% CI 0.55 to 0.81) and the evidence for other calcium agonists was not statistically significant.

**Conclusion:** The authors endorse the use of oral nimodipine in patients with aneurysmal subarachnoid hemorrhage.



### “Triple H” Therapy for Vasospasm

Hypertension  
Hypervolemia  
Hemodilution



### Magnesium for Aneurysmal Subarachnoid Hemorrhage (MASH-2): A Randomized Placebo-Controlled Trial

*Lancet* 2012;380:44-49

**Introduction:** MgSO<sub>4</sub> is a neuroprotective agent that may improve outcomes after SAH.

**Methods:** Phase 3 multicentre, international, randomized, placebo-controlled trial of adults with SAH on imaging comparing either IV MgSO<sub>4</sub> or placebo treatment. Primary outcome was poor outcome rated on a score of 4-5 on Rankin score or death at 3 mo after SAH.

**Results:** 2.6.2% of patients had poor outcome in the magnesium group compared to 25.3% of patients in the placebo group.

**Conclusions:** IV MgSO<sub>4</sub> does not improve clinical outcome after aneurysmal SAH.

# Intracerebral Hemorrhage (ICH)



## Definition

- hemorrhage within brain parenchyma, accounts for ~10% of strokes
- can dissect into ventricular system (IVH) or through cortical surface (SAH)

## Etiology

- HTN (usually causes bleeds at putamen, thalamus, pons and cerebellum)
- hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
- vascular anomalies
  - aneurysm, AVMs, and other vascular malformations (see *Vascular Malformations*, NS23)
  - venous sinus thrombosis
  - arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
- tumours (1%): often malignant (e.g. GBM, lymphoma, metastases)
- drugs (amphetamines, cocaine, alcohol, anticoagulants, etc.)
- coagulopathy (iatrogenic, leukemia, TTP, aplastic anemia)
- CNS infections (fungal, granulomas, herpes simplex encephalitis)
- post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
- eclampsia
- post-operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
- idiopathic

**Epidemiology**

- 12-15 cases/100,000 population/yr

**Risk Factors**

- increasing age (mainly >55 yr)
- male gender
- HTN
- Black/Asian > Caucasian
- previous CVA of any type (23x risk)
- both acute and chronic heavy alcohol use; cocaine, amphetamines
- liver disease
- anticoagulants

**Clinical Features**

- TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
- location: basal ganglia/internal capsule (50%), thalamus (15%), cerebral white matter (15%), cerebellum/brainstem – usually pons (15%)
- gradual onset of symptoms over minutes-hours, usually during activity
- H/A, N/V, and decreased LOC are common
- specific symptoms/deficits depend on location of ICH

**Investigations**

- hyperdense blood on non-contrast CT
- CTA routine, if spot sign demonstrated there is high likelihood of clot growth

**Treatment**

- medical
  - decrease MAP to pre-morbid level or by ~20% (target BP 140/90)
  - check PTT/INR, and correct coagulopathy
  - control raised ICP (see *Intracranial Pressure Dynamics*, NS4)
  - levetiracetam/phenytoin for seizure prophylaxis
  - follow electrolytes (SIADH common)
  - angiogram to r/o vascular lesion unless >45 yr, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~0%)
- surgical
  - craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
  - indications
    - ♦ symptoms of raised ICP or mass effect
    - ♦ rapid deterioration (especially if signs of brainstem compression)
    - ♦ favourable location (e.g. cerebellar, non-dominant hemisphere)
    - ♦ young patient (<50 yr)
    - ♦ if tumour, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)
  - contraindications
    - ♦ small bleed: minimal symptoms, GCS >10
    - ♦ poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
    - ♦ medical reasons [e.g. very elderly, severe coagulopathy, difficult location (e.g. basal ganglia, thalamus)]

**Prognosis**

- 30-d mortality rate 44%, mostly due to cerebral herniation
- rebleed rate 2-6%, higher if HTN poorly controlled

## Intracranial Aneurysms

**Epidemiology**

- prevalence 1-4% (20% have multiple)
- female > male; age 35-65 yr

**Risk Factors**

- autosomal dominant polycystic kidney disease (15%)
- fibromuscular dysplasia (7-21%)
- AVMs
- connective tissue diseases (Ehlers-Danlos, Marfan)
- family history
- bacterial endocarditis
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- atherosclerosis and HTN
- trauma

**Types** (for location, see Figure 4, NS3)

- saccular (berry)
  - most common type
  - located at branch points of major cerebral arteries (Circle of Willis)
  - 85-95% in carotid system, 5-15% in vertebrobasilar circulation
- fusiform
  - atherosclerotic
  - more common in vertebrobasilar system, rarely rupture
- infectious
  - secondary to any infection of vessel wall, 20% multiple
  - 60% *Streptococcus* and *Staphylococcus*
  - 3-15% of patients with bacterial endocarditis

**Table 10. 5-year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location**

	Cavernous Carotid	AC/MC/IC	Vertebrobasilar/PC/PComm
<7 mm	0%	0%	2.5%
7-12 mm	0%	2.6%	14.5%
13-24 mm	3%	14.5%	18.4%
≥24 mm	6.4%	40%	50%

AC – anterior cerebral/anterior communicating artery; MC – middle cerebral artery; IC – internal carotid artery; PC – posterior cerebral artery; PComm – posterior communicating artery  
*The Lancet* 2003;362:103-10

### Clinical Presentation

- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage (“thunderclap H/A”) → requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  - internal carotid or anterior communicating aneurysm may compress:
    - ♦ the pituitary stalk or hypothalamus causing hypopituitarism
    - ♦ the optic nerve or chiasm producing a visual field defect
  - basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
  - posterior communicating artery aneurysm may produce CN III palsy
  - intracavernous aneurysms (CN III, IV, V<sub>1</sub>, V<sub>2</sub>, VI)
- distal embolization (e.g. amaurosis fugax)
- seizures
- headache (without hemorrhage)
- incidental CT or angiography finding (asymptomatic)

### Investigations

- CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

### Treatment

- ruptured aneurysms
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
  - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling), wrapping (last resort)
  - choice of surgery vs. coiling not yet well defined, consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition. In general:
    - ♦ coiling: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    - ♦ clipping: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- unruptured aneurysms
  - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  - no clear evidence on when to operate: need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20%-50%) vs. surgical risk (2%-5%)
  - generally treat unruptured aneurysms >10 mm
  - consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
  - follow smaller aneurysms with serial angiography



#### Commonest Locations of Saccular Aneurysms

- AComm: 30%
- PComm: 25%
- MCA: 20%
- Basilar tip: 7%



#### Risk of Recurrent Subarachnoid Haemorrhage, Death, or Dependence and Standardised Mortality Ratios after Clipping or Coiling of an Intracranial Aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): Long-Term Follow-Up

*Lancet Neurol* 2009;8:427-433

**Objective:** To assess the long-term risk of death, disability, and rebleeding in patients randomly assigned to clipping or endovascular coiling after rupture of an intracranial aneurysm in the follow-up of the ISAT trial

**Methods:** Randomized controlled trial comparing endovascular coiling treatment with craniotomy and clipping for ruptured intracranial aneurysms in 2143 patients who were considered eligible for either modality of therapy. Annual follow-up was done for a mean length of 9 yr to assess long-term survival and dependency.

**Results:** 10 patients in the coiled group and 3 patients in the clipped group had rebled from the original aneurysm. In patients with ruptured intracranial aneurysms suitable for both treatments, the survival rate at 5 yr after endovascular coiling was higher at 89% vs 86% for neurosurgical clipping (relative risk 0.77,  $p=0.03$ ). The likelihood of independence at 5 yr following treatment is the same for both groups (83% for coiling vs 82% for clipping).

**Conclusions:** The risk of death at 5 yr was significantly lower in the coiled group than it was in the clipped group. There was a small increased risk of recurrent bleeding from a coiled aneurysm compared with a clipped aneurysm.



#### Unruptured Intracranial Aneurysms – Risk of Rupture and Risks of Surgical Intervention. International Study of Unruptured Intracranial Aneurysms Investigators

*NEJM* 1998;339:1725-33

**Introduction:** The management of unruptured intracranial aneurysms requires knowledge of the natural history of these lesions.

**Methods:** Retrospective and prospective, multicenter, international study of 2621 patients with unruptured intracranial aneurysms.

**Results:** In patients with no previous history of aneurysm rupture, cumulative rate of rupture of aneurysms less than 10 mm was less than 0.05% and for aneurysms greater than 10 mm was less than 1%. However, giant aneurysms >25 mm had a 6% risk of rupture within 1 yr. In patients with a previous history of aneurysm bleed from a different aneurysm, the risk of rupture for aneurysms <10 mm was 0.5% and for aneurysms >10 mm was less than 1%.

**Conclusions:** Surgery is unlikely to reduce rates of morbidity and mortality in patients with unruptured intracranial aneurysms smaller than 10 mm in diameter and no history of subarachnoid hemorrhage. In these patients, the morbidity and mortality related to surgery greatly exceeded the 7.5 yr risk of rupture for aneurysms <10 mm.

## Carotid Stenosis

### Definition

- narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids

### Risk Factors

- for atherosclerosis: HTN, smoking, DM, CVD or CAD, dyslipidemia

### Clinical Features

- may be asymptomatic
- symptomatic stenosis may present as TIA, reversible ischemic neurologic deficit (RIND), or stroke
- retinal insufficiency or infarct permanently or temporarily (amaurosis fugax), (see [Ophthalmology](#), OP37)
- middle cerebral artery (MCA) occlusive symptoms

### Investigations

- CBC, PTT/INR (hypercoagulable states)
- fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)
- auscultation over carotid bifurcation for bruits (do not correlate with degree of stenosis)
- carotid duplex: determines severity of disease (mild/moderate/severe stenosis or occlusion)
- angiogram: "gold standard" but invasive and 1/200 risk of stroke (not for screening)
- MRA: safer than angiogram, may overestimate stenosis

### Treatment

- control of HTN, lipids, diabetes
- antiplatelet agents (ASA ± dipyridamole, clopidogrel) ~25% relative risk reduction
- carotid endarterectomy (generally if symptomatic and >70% stenosis, see Tables 11 and 12)
- endovascular angioplasty ± stenting

### Prognosis

**Table 11. Symptomatic Carotid Stenosis: North American Symptomatic Carotid Endarterectomy Trial (NASCET)**

% Stenosis on Angiogram	Risk of Major Stroke or Death	
	Medical Rx	Medical + Surgical Rx
70-99%	26% over 2 yr	9% over 2 yr
50-69%	22% over 5 yr	16% over 5 yr
<50%	Surgery has no benefit with 5% complication rate	

**Table 12. Asymptomatic Carotid Stenosis: Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST)**

% Stenosis on Angiogram	Risk of Major Stroke or Death	
	Medical Rx	Medical + Surgical Rx
60-99%	11% over 5 yr	5.1% over 5 yr (ACAS)
50-69%	11.8% over 5 yr	6.4% over 5 yr (ACST)



#### Prevention of Disabling and Fatal Strokes by Successful Carotid Endarterectomy in Patients Without Recent Neurological Symptoms: Randomized Controlled Trial

*Lancet* 2004;363:1491-1502

**Study:** Asymptomatic Carotid Surgery Trial (ACST), a RCT with follow-up at 5 yr.

**Patients:** 3120 asymptomatic patients with significant carotid artery stenosis were randomized equally between immediate carotid endarterectomy (CEA) and indefinite deferral of CEA and were followed for up to 5 yr (mean 3.4 yr).

**Main Outcome:** Any stroke (including fatal or disabling).

**Conclusions:** In asymptomatic patients with significant carotid artery stenosis, immediate CEA reduced the net 5-yr stroke risk from about 12% to about 6%. Half of this 5-yr benefit involved disabling or fatal strokes.



#### Spetzler-Martin AVM Grading Scale

Item	Score
<b>Size</b>	
0-3 cm	1
3.1-6.0 cm	2
> 6 cm	3
<b>Location</b>	
Noneloquent	0
Eloquent	1
<b>Deep venous drainage</b>	
Not present	0
Present	1

AVM grades calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table. e.g. a 2 cm tumour in noneloquent location without deep venous drainage = Grade I

## Vascular Malformations

### Types

- arteriovenous malformations (AVMs)
- cavernous malformations (= cavernomas, cavernous hemangiomas/angiomas)
- venous angioma
- capillary telangiectasias
- arterio-venous fistula (AVF) (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- "angiographically occult vascular malformations" (any type, 10% of malformations)

## Arteriovenous Malformations (AVMs)

### Definition

- tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma, usually congenital

### Epidemiology

- prevalence ~0.14%, male:female = 2:1, average age at diagnosis = 33 yr
- 15-20% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs



### Clinical Features

- hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections
- seizures (50%): more common with larger AVMs
- mass effect
- focal neurological signs secondary to ischemia (high flow → “steal phenomena”)
- localized headache, increased ICP
- bruit (especially with dural AVMs)
- may be asymptomatic (“silent”)

### Investigations

- MRI (flow void), MRA
- angiography (7% will also have one or more associated aneurysms)

### Treatment

- decreases risk of future hemorrhage and seizure
  - surgical excision is treatment of choice
  - SRS is preferred for small (<3 cm) or very deep lesions
  - endovascular embolization (glue, balloon) can facilitate surgery or SRS for larger lesions
- conservative (e.g. palliative embolization, seizure control if necessary)

### Prognosis

- 10% mortality, 30-50% morbidity (serious neurological deficit) per bleed
- risk of major bleed in untreated AVMs: 2-4% per year

## Cavernous Malformations

- benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins
- several genes now described: CCM1, CCM2, CCM3
- prevalence of 0.1-0.2%, both sporadic and hereditary forms described

### Clinical Features

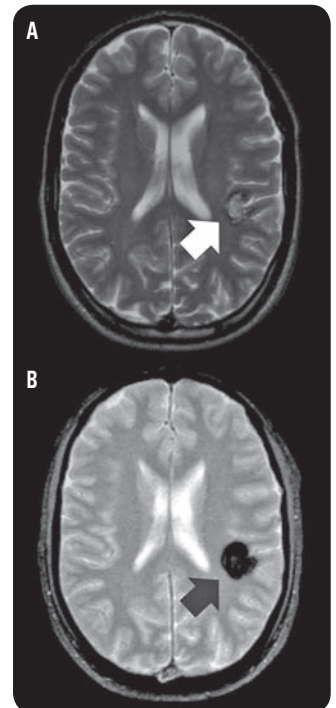
- seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A
- often an incidental finding
- hemorrhage risk less than AVM, usually minor bleeds

### Investigations

- T2WI MRI (non-enhancing; see Figure 19) gradient echo sequencing (best for diagnosis)

### Treatment

- surgical excision
  - only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions)



**Figure 19. MRI of cavernous malformation**

A. T2 weighted imaging MRI

B. Gradient echo sequencing MRI



#### Stereotactic Radiosurgery for Cavernous Malformations

*J Neurosurg* 2000;93:987-991

**Introduction:** The use of radiosurgery for treatment of cerebral cavernous malformations (CM) is controversial. The safety and efficacy of CM radiosurgery is described.

**Methods:** Retrospective review of 17 patients with CM who underwent radiosurgery over a 10-yr period. All patients had at least 2 documented hemorrhages prior to therapy.

**Results:** Annual hemorrhage rate 51 mo preceding surgery was 40.1% compared to 8.8% in first 2 yr after radiosurgery and 2.9% thereafter. However, 41% of patients developed a permanent radiation-related morbidity.

**Conclusions:** Impossible to conclude that radiosurgery protects patients with CMs against future hemorrhage.



#### RED FLAGS for Back Pain

##### BACK PAIN

**Bowel/Bladder** (retention or incontinence)

**Anesthesia** (saddle)

**Constitutional symptoms**

**Chronic disease**

**Parasthesia**

**Age >50 or <20**

**IV drug use**

**Neuromotor deficits**

##### Cauda Equina

- Urinary retention or incontinence, fecal incontinence or loss of anal sphincter tone, saddle anesthesia, uni/bilateral, leg weakness/pain

##### Malignancy

- Age >50, previous hx of cancer, pain unrelieved by bed rest, constitutional symptoms

##### Infection

- Increased ESR, IV drug use, immunosuppressed, fever

##### Compression Fracture

- Age >50, trauma, prolonged steroid use

## EXTRACRANIAL PATHOLOGY



## Approach to Limb/Back Pain

- see [Orthopedics](#), OR21

## Extradural Lesions

### Root Compression

#### Differential Diagnosis

- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

## Cervical Disc Syndrome

#### Etiology

- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C6-C7 (C7 root)



### Clinical Features

- pain down arm in nerve root distribution, worse with neck extension, ipsilateral rotation and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

### Investigations

- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- only consider EMG, nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue.

### Treatment

- conservative
  - no bedrest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics, NSAIDs are more efficacious
  - avoid cervical manipulation, like traction
- surgical indications
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurological deficit
  - anterior cervical discectomy is usual surgical choice

### Prognosis

- 95% improve spontaneously in 4-8 wk

**Table 13. Lateral Cervical Disc Syndromes**

	C4-5	C5-6	C6-7	C7-T1
<b>Root Involved</b>	C5	C6	C7	C8
<b>Incidence</b>	2%	19%	69%	10%
<b>Sensory</b>	Shoulder	Thumb	Middle finger	Ring finger, 5th finger
<b>Motor</b>	Deltoid, biceps, supraspinatus	Biceps	Triceps	Digital flexors, intrinsic
<b>Reflex</b>	No change	Biceps, brachioradialis	Triceps	Finger jerk (Hoffmann's sign)



Disc herniations impinge the nerve root at the level below the interspace (i.e. C5-6 disc affects the C6 nerve root).

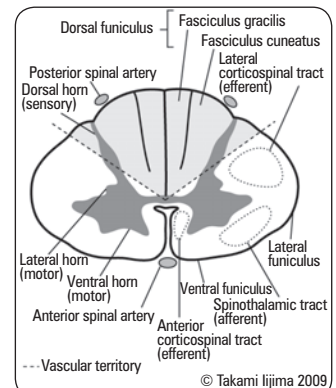


#### Sensory Fibres

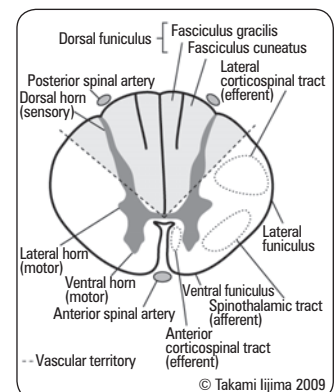
Fasciculus gracilis/cuneatus: joint position, fine touch, vibration  
Spinothalamic tract: pain and temperature

#### Motor Fibres

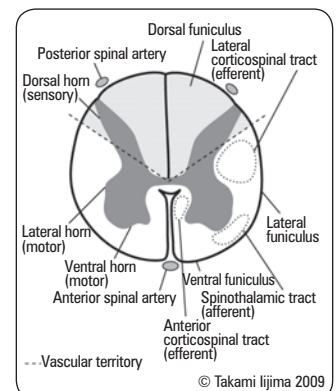
Corticospinal tract: skilled movements



**Figure 20A. Axial section of cervical spine with vascular and functional territories**



**Figure 20B. Axial section of thoracic spine with vascular and functional territories**



**Figure 20C. Axial section of lumbar spine with vascular and functional territories**

## Cervical Stenosis (Cervical Spondylosis)

### Definition

- cervical spondylosis is chronic disc degeneration and associated facet arthropathy
- resultant syndromes include mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression), and combinations

### Epidemiology

- typically begins at age 40-50, male > female, most commonly at the C5-C6 > C6-C7 levels

### Pathogenesis

- cervical stenosis leading to spinal cord compression and myelopathy is a serious and common issue
- pathophysiology includes static compression, dynamic compression and vascular compromise

### Clinical Features

- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling's test)
- occipital headache is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder and arm pain, paresthesias and numbness
- cervical myelopathy may be characterized by weakness (upper > lower extremity), decreased dexterity, and sensory changes
- UMN findings such as hyperreflexia, clonus and Babinski reflex may be present
- most worrisome complaint is lower extremity weakness (corticospinal tracts)
- myelopathy may be associated with funicular pain, characterized by burning and stinging ± Lhermitte's sign (lightning-like sensation down the back with neck flexion)

### Investigations

- x-ray of cervical spine ± flexion/extension (alignment, fractures)
- MRI most useful for determination of compression of the neural element
- CT is only used for better determination of bony anatomy (i.e. OPLL)
- EMG/nerve conduction studies reserved for peripheral nerve investigation

### Treatment

- decompression and stabilization need to be included in the management
- NSAIDs, moist heat, strengthening and range of motion exercises, analgesics, cervical collar, cervical traction
- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain

## Lumbar Disc Syndrome

### Etiology

- posteriolaterally herniated disc compressed nerve root exiting **BELOW** the level of the disc or the traversing nerve root
- far lateral disc herniation compressed nerve root **AT** the level of the disc or the exiting nerve root
- central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

### Clinical Features

- initially back pain, then leg pain > back pain
- limited back movement (especially forward flexion) due to pain
- motor weakness, dermatomal sensory changes, decreased reflexes
- exacerbation with coughing, sneezing or straining. Relief with flexing the knee or thigh
- nerve root tension signs
  - straight leg raise (SLR: Lasegue's test) or crossed SLR (pain should occur at less than 60 degrees) suggests L5, S1 root involvement
  - femoral stretch test suggests L2, L3 or L4 root involvement

### Investigations

- MRI is modality of choice
- x-ray spine (only to rule out other lesions), CT (bony anatomy)
- myelogram and post-myelogram CT (only if MRI is contraindicated)

### Treatment

- conservative (same as cervical disc disease)
- surgical indications
  - same as cervical disc + cauda equina syndrome

### Prognosis

- 95% improve spontaneously within 4 to 8 wk
- do not follow patients with serial MRIs. Clinical status is more important at guiding management

**Table 14. Lateral Lumbar Disc Syndromes**

	L3-4	L4-5	L5-S1
<b>Root Involved</b>	L4	L5	S1
<b>Incidence</b>	<10%	45%	45%
<b>Pain</b>	Femoral pattern	Sciatic pattern	Sciatic pattern
<b>Sensory</b>	Medial leg	Dorsal foot to hallux Lateral leg	Lateral foot
<b>Motor</b>	Tibialis anterior (dorsiflexion)	Extensor hallucis longus (hallux extension)	Gastrocnemius, soleus (plantar flexion)
<b>Reflex</b>	Knee jerk	Medial hamstrings	Ankle jerk

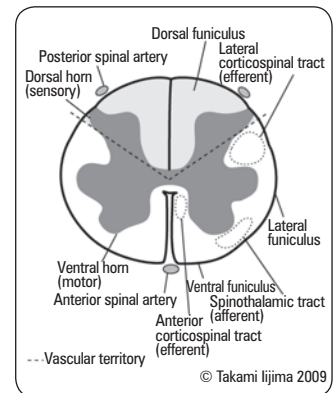
**Table 15. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome**

	Conus Medullaris Syndrome	Cauda Equina Syndrome
<b>Onset</b>	Sudden, bilateral	Gradual, unilateral
<b>Spontaneous Pain</b>	Rare, if present usually bilateral, symmetric in perineum or thighs	Severe, radicular type: in perineum, thighs, legs, back, or bladder
<b>Sensory Deficit</b>	Saddle; bilateral and symmetric; sensory dissociation	Saddle; no sensory dissociation; may be unilateral and asymmetric
<b>Motor Deficit</b>	Symmetric; paresis less marked; fasciculations may be present	Asymmetric; paresis more marked; atrophy may be present; fasciculations rare
<b>Reflexes</b>	Only ankle jerk absent (preserved knee jerk)	Knee and ankle jerk may be absent
<b>Autonomic Symptoms (bladder dysfunction, impotence, etc.)</b>	Urinary retention and atonic anal sphincter prominent early; impotence frequent	Sphincter dysfunction presents late; impotence less frequent

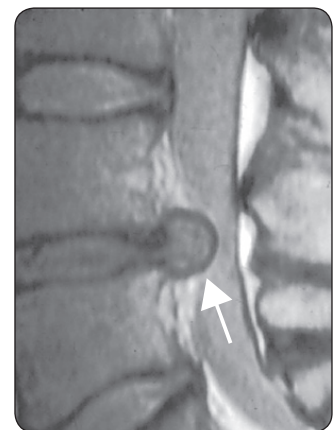
## Cauda Equina Syndrome

### Etiology

- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumour



**Figure 20D. Axial section of sacral spine with vascular and functional territories**



**Figure 21. T2-weighted MRI of lumbar disc herniation**



### Magnetic Resonance Imaging in Follow-up Assessment of Sciatica

NEJM 2013;368:999-1007

**Background:** Follow-up MRI is a controversial method for monitoring sciatica in patients with known lumbar-disk herniation.

**Methods:** Participants (n=283) were recruited from a simultaneous, parallel, randomized study comparing surgery and conservative care for sciatica (the Sciatica Trial). MRI and clinical assessment were undertaken pre-treatment and 1 yr post-treatment randomization to visualize disk herniation and evaluate outcome.

**Results:** At 1 yr, disk herniation was visible in 35% with a favorable outcome (complete, or nearly complete symptom resolution) and in 33% with an unfavorable outcome (p=0.70). A favorable outcome was reported in 85% of patients with disk herniation and 83% without disk herniation (p=0.70).

**Conclusions:** Anatomical abnormalities visible on repeated MRI 1 yr after treatment for sciatica due to lumbar-disk herniation could not distinguish patients with resolution of their symptoms from patients still experiencing symptoms.

**Clinical Features**

- usually acute (develops in less than 24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness/paraparesis in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
  - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
  - bilateral sensory loss or pain: depends on the level affected
  - saddle area (S2-S5) anesthesia
  - sexual dysfunction (late finding)

**Investigations**

- urgent MRI to confirm compression of S2-3-4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present. Volumes controversial but anything over 250 cc in a healthy individual is cause for concerns

**Treatment**

- surgical decompression (<48 h) to preserve bowel, bladder and sexual function, and/or to prevent progression to paraplegia

**Prognosis**

- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

## Lumbar Spinal Stenosis

**Etiology**

- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

**Clinical Features**

- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

**Investigations**

- MRI is the optimal investigation to confirm and localize the level of stenosis. Unlike nerve root compression which can be localized with clinical exam this is more difficult and requires imaging

**Treatment**

- conservative: NSAIDs, analgesia
- surgical: laminectomy with root decompression (the role of fusion may need to be considered if the amount of bone removed with the laminectomy results in de-stabilization)

## Neurogenic Claudication

**Etiology**

- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

**Clinical Features**

- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

**Investigations**

- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

**Treatment**

- same as for lumbar spinal stenosis

**Key Features of Neurogenic vs. Vascular Claudication**

**Neurogenic Claudication:** dermatomal distribution with positional relief occurring over minutes.

**Vascular Claudication:** sclerotomal distribution with relief occurring with rest over seconds.

# Intradural Intramedullary Lesions

## Syringomyelia (Syrinx)



### Definition

- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over months to years
- initially pain, weakness; later atrophy and loss of pain and temperature sensation

### Etiology

- 70% are associated with Chiari I malformation, 10 % with basilar invagination
- post-traumatic
- tumour
- tethered cord

### Clinical Features

- nonspecific features for any intramedullary spinal cord pathology:
  - initially pain, weakness, atrophy, loss of pain and temperature in upper extremities (central syrinx) with progressive myelopathy over years
  - sensory loss with preserved touch and joint position sense in a band-like distribution at the level of cervical syrinx
  - sensory loss: suspended dissociated sensory loss may result in painless ulcerations and/or burns
  - dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - painless neuropathic arthropathies (Charcot's joints), especially in the shoulder and neck due to loss of pain and temperature sensation (seen in less than 5%)



Figure 22. T1 Weighted MRI of syringomyelia

### Investigations

- MRI is best method, myelogram with delayed CT

### Treatment

- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)
- rarely does the syrinx need to be shunted, only when progressive and size allows for insertion of tube

# Spinal Cord Syndromes

- see [Neurology](#), N4, for spinal cord anatomy
- Spinal cord injury impairment classified according to ASIA score
- ASIA A: complete, no motor/sensory below neurological level including S4/5
- ASIA B: incomplete, sensory but not motor function preserved below neurological level including S4/5
- ASIA C: incomplete, motor function preserved below neurological level and more than half of the key muscles below neurological level have a muscle grade <3
- ASIA D: incomplete, motor function preserved below neurological level and more than half of the key muscles below neurological level have a muscle grade 3 or more
- ASIA E: normal motor and sensory function

### Complete Spinal Cord Lesion

- bilateral loss of motor/sensory and autonomic function at  $\geq 4$  segments below lesion/injury, with UMN signs
- about 3% of patients with complete injuries will develop some recovery within 24 h, beyond 24 h, no distal function will recover

### Incomplete Spinal Cord Lesion

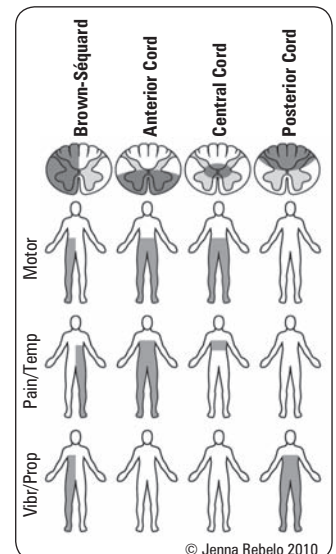
- any residual function at  $\geq 4$  segments below lesion
- signs include sensory/motor function in lower limbs and "sacral sparing" (perianal sensation, voluntary rectal sphincter contraction)



Compartmentalize spinal cord syndromes anatomically by location.

**Table 16. Comparison between Incomplete Spinal Cord Lesion Syndromes**

Syndrome	Etiology	Motor	Sensory
<b>Brown-Séquard</b>	Hemisection of cord	Ipsilateral LMN weakness at the lesion Ipsilateral UMN weakness below the lesion	Ipsilateral loss of vibration and proprioception Contralateral loss of pain and temperature Preserved light touch
<b>Anterior Cord</b>	Anterior spinal artery compression or occlusion	Bilateral LMN weakness at the lesion Bilateral UMN weakness below the lesion Urinary retention	Preserved vibration and proprioception Bilateral loss of pain and temperature Preserved light touch
<b>Central Cord</b> (most common)	Syringomyelia, tumours, spinal hyperextension injury	Bilateral motor weakness: Upper limb weakness (LMN lesion) greater than Lower limb weakness (UMN lesion) Urinary retention	Variable bilateral suspended sensory loss Loss of pain and temperature greater than loss of vibration and proprioception
<b>Posterior Cord</b>	Posterior spinal artery infarction, trauma	Preserved	Bilateral loss of vibration, proprioception, light touch at and below the lesion Preserved pain and temperature

**Figure 23. Spinal cord lesion syndromes**

- see [Neurology](#), N31 and [Plastic Surgery](#), PL28

### Seddon's Classification of Peripheral Nerve Injury

- class I: **neurapraxia** – axon structurally intact but fails to function; recovery within hours to months (average 6-8 wk)
- class II: **axonotmesis** – axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury → spontaneous axonal recovery at 1 mm/d, max at 1-2 yr
- class III: **neurotmesis** – nerve completely transected, need surgical repair for possibility of recovery
- etiologies: ischemia, nerve entrapment – nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve

### Investigations

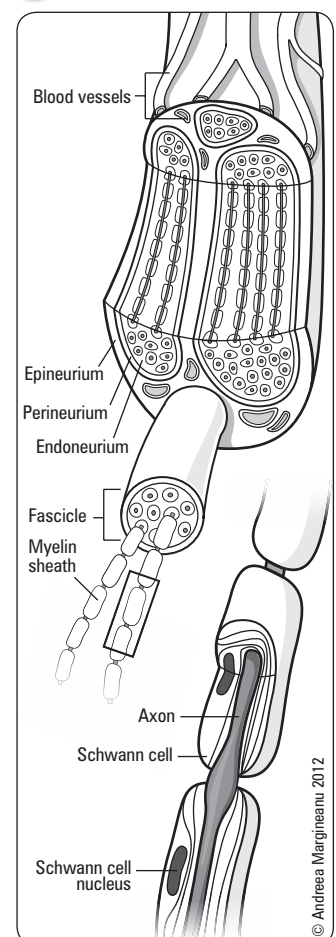
- neurological exam (power, sensation, reflexes), localization via Tinel's sign (paresthesias elicited by tapping along the course of a nerve)
- electrophysiological studies (EMG, nerve conduction study) may be helpful in assessing nerve integrity and monitoring recovery, not helpful until 2-3 wk post-injury
- labs: bloodwork, CSF
- imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography, identify etiology
- angiogram if vascular damage is suspected

### Treatment

- early neurosurgical consultation if injury is suspected
- entrapment
  - conservative: prevent repeated stress/injury, physiotherapy, NSAIDs, local anaesthesia/steroid injection
  - surgical: nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management
- stretch/contusion
  - follow-up clinically for recovery; exploration if no recovery in 3 mo
- axonotmesis
  - if no evidence of recovery, resect damaged segment
  - prompt physical therapy and rehabilitation to increase muscle function, maintain joint range of motion, and maximize return of useful function
  - recovery usually incomplete
- neurotmesis
  - surgical repair of nerve sheath unless known to be intact [suture nerve sheaths directly if ends approximate or nerve graft (usually sural nerve)]
  - clean laceration: early exploration and repair
  - contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 d

### Complications

- neuropathic pain: with neuroma formation
- complex regional pain syndrome: with sympathetic nervous system involvement

**Figure 24. Peripheral nerve structure**



## SPECIALTY TOPICS

### Neurotrauma

**Trauma Management** (see also [Emergency Medicine](#), ER6)

#### Indications for Intubation in Trauma

1. depressed LOC (patient cannot protect airway): usually GCS  $\leq 8$
2. need for hyperventilation
3. severe maxillofacial trauma: patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management
  - if basal skull fracture suspected, use orotracheal instead of nasotracheal intubation
  - note: intubation prevents patient's ability to verbalize for determining GCS

### Trauma Assessment

#### INITIAL MANAGEMENT

##### ABCs of Trauma Management

- see [Emergency Medicine](#), ER8

#### NEUROLOGICAL ASSESSMENT

##### Mini-History

- period of LOC, post-traumatic amnesia, loss of sensation/function, type of injury/accident

##### Neurological Exam

- Glasgow Coma Scale (GCS)
- head and neck (lacerations, bruises, basal skull fracture signs, facial fractures, foreign bodies)
- spine (palpable deformity, midline pain/tenderness)
- eyes (pupillary size and reactivity)
- brainstem (breathing pattern, CN palsies)
- cranial nerve exam
- motor exam, sensory exam (only if GCS is 15), reflexes
- sphincter tone
- record and repeat neurological exam at regular intervals

##### Investigations

- spinal injury precautions (cervical collar) are continued until C-spine is cleared
- C,T,L-spine x-rays
  - AP, lateral, odontoid views for C-spine (must see from C1 to T1; swimmer's view if necessary) or CT
  - rarely done: oblique views looking for pars interarticularis fracture ("Scottie dog" sign)
- CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
- cross and type, ABG, CBC, drug screen (especially alcohol)
- chest and pelvic x-ray as indicated

#### TREATMENT

##### Treatment for Minor Head Injury

- observation over 24-48 h
- wake every hour
- judicious use of sedatives or pain killers during monitoring period

##### Treatment for Severe Head Injury (GCS $\leq 8$ )

- clear airway and ensure breathing (if GCS  $\leq 8$ , intubate)
- secure C-spine
- maintain adequate BP
- monitor for clinical deterioration
- monitor and manage increased ICP if present (see *Herniation Syndromes*, NS7)

##### Admission required if:

- skull fracture (indirect signs of basal skull fracture, see *Head Injury*, NS31)
- confusion, impaired consciousness, concussion with  $>5$  min amnesia
- focal neurological signs, extreme headache, vomiting, seizures
- unstable spine
- use of alcohol
- poor social support



#### Glasgow Coma Scale

Eye Response	Verbal Response	Motor Response
4 spontaneous	5 oriented	6 obeys commands
3 opens eyes to voice	4 confused	5 localizes to pain
2 opens eyes to pain	3 inappropriate words	4 withdraws from pain
1 no eye opening	2 incomprehensible sounds	3 flexion to pain (decorticate posturing)
	1 no response	2 extension to pain (decerebrate posturing)
	T intubated	1 no response

Best response for each component recorded individually (e.g. E3V3M5)  
 $\geq 13$  is mild injury; 9-12 is moderate injury;  $\leq 8$  is severe injury



#### Assessment of Spine CT/X-ray (parasagittal view)

##### ABCDs

**Alignment** (Columns: anterior vertebral line, posterior vertebral line, spinolaminar line, posterior spinous line)  
**Bone** (vertebral bodies, facets, spinous processes)  
**Cartilage**  
**Disc** (disc space and interspinous space)  
**Soft tissues**



#### The Canadian CT Head Rule for Patients with Minor Head Injury

*The Lancet* 2001;357:1391-1396

**CT Head is only required for patients with minor head injuries with any one of the following:**

##### High risk (for neurological intervention)

- GCS score  $<15$  at 2 h after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture (hemotympanum, "raccoon" eyes, cerebrospinal fluid otorrhea/rhinorrhea, Battle's sign)
- Vomiting  $\geq 2$  episodes
- Age  $\geq 65$  yr

##### Medium risk (for brain injury on CT)

- Amnesia after impact  $>30$  min
- Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height  $>3$  feet or five stairs)

**Minor head injury** is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.



- Never do lumbar puncture in head injury unless increased ICP has been ruled out
- All patients with head injury have C-spine injury until proven otherwise
- Suspect hematoma in alcoholic-related injuries
- Low BP after head injury means injury elsewhere
- Must clear spine both radiologically AND clinically



## Head Injury

### Epidemiology

- male to female: 2-3:1

### Pathogenesis

- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

### Scalp Injury

- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

### Skull Fractures

- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
  - internal fractures into sinus may lead to meningitis, pneumocephalus
  - risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray, rely on clinical signs
  - retroauricular ecchymoses (Battle's sign)
  - periorbital ecchymoses (raccoon eyes)
  - hemotympanum
  - CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

### Cranial Nerve Injury

- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VIII: repair of ossicles
- CN injuries that improve
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
  - CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

### Arterial Injury

- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

### Intracranial Bleeding

- see *Blood*, NS16 and *Cerebrovascular Disease*, NS18



#### A Trial of Intracranial-Pressure Monitoring in Traumatic Brain Injury *NEJM* 2012;367:2471-2481

**Background:** ICP monitoring is frequently used to monitor severe traumatic brain injury, but controversy exists over whether it is beneficial.

**Methods:** Study sample (n=324 patients, aged 13 yr or older) consisted of those who had severe traumatic brain injury and were being treated in ICU in Bolivia or Ecuador. Patients were randomly assigned to one management group:

1. ICP-monitoring based management or
2. management based on imaging and clinical examination.

Primary outcome was a composite of survival time, impaired consciousness, functional status (at 3, 6 mo), and neuropsychological status (at 6 mo).

**Results:** No significant difference between management groups based on primary outcome, 6-mo mortality, median length of ICU stay, or occurrence of serious adverse events. However, duration of brain-specific treatments (e.g. use of hyperosmolar fluids or hyperventilation) higher in the imaging-clinical examination group (4.8 d vs. 3.4 d, p=0.002).

**Conclusion:** Maintaining monitored ICP at 20 mmHg or less is not superior to care based on imaging and clinical examination.



#### AAN Classification

- Grade 1: altered mental status <15 min
- Grade 2: altered mental status >15 min
- Grade 3: any loss of consciousness

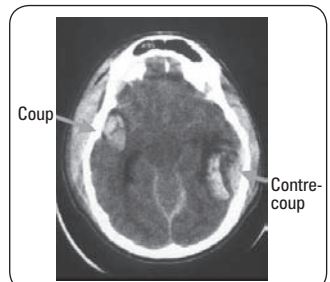
See sidebar on NS32 for management by classification



## Brain Injury

### Primary Impact Injury

- mechanism of injury determines pathology: penetrating injuries, direct impact
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- concussion:** a trauma-induced alteration in mental status
  - American Academy of Neurology (AAN) Classification (see sidebar)
  - no parenchymal abnormalities on CT
- coup** (damage at site of blow) and **contrecoup** (damage at opposite site of blow) (see Figure 25)
  - acute decompression causes cavitation followed by a wave of acute compression
- contusion** (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing**
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space occupying lesion on CT



**Figure 25. CT showing coup-contrecoup injury**

## Secondary Pathologic Processes

- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to
  - high glutamate release → NMDA → cytotoxic cascade
  - cerebral edema
  - intracranial hemorrhages
  - ischemia/infarction
  - raised ICP, intracranial HTN
  - hydrocephalus

## Extracranial Conditions

- hypoxemia
  - due to trauma to the chest, upper airway, brainstem
  - extremely damaging to vulnerable brain cells
  - leads to ischemia, raised ICP
- hypercarbia
  - leads to raised ICP (secondary to vasodilation)
- systemic hypotension
  - caused by blood loss (e.g. ruptured spleen)
  - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
  - leads to increased brain metabolic demands → ischemia
- fluid and electrolyte imbalance
  - iatrogenic (most common)
  - SIADH caused by head injury
  - diabetes insipidus (DI)
  - may lead to cerebral edema and raised ICP
- coagulopathy

## Intracranial Conditions

- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

## Brain Injury Outcomes

- mildly traumatic (GCS 13-15): post-concussive symptoms: H/A, fatigue, dizziness, nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
- moderately traumatic (GCS 9-12): proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age



SIADH → hyponatremia  
DI → hypernatremia



### Management Associated with AAN Concussion Grades

AAN Grade	Management Options
1	<ul style="list-style-type: none"> <li>• Examine 15 min for amnesia and other symptoms</li> <li>• Return to normal activity if symptoms clear within 15 min</li> </ul>
2	<ul style="list-style-type: none"> <li>• Remove from activity for 1 d, then reexamine</li> <li>• CT or MRI if H/A or other symptoms worsen or last &gt; 1 wk</li> <li>• Return to normal activity after 1 wk without symptoms</li> </ul>
3	<ul style="list-style-type: none"> <li>• Emergent neuro exam + imaging; if initial exam is normal, may go home with close follow up</li> <li>• Admit if any signs of pathology or persistent abnormal mental status</li> <li>• CT or MRI if H/A or other symptoms</li> <li>• If brief loss of consciousness (&lt; 1 min), return to normal activity after 1 wk without symptoms</li> <li>• If prolonged loss of consciousness (&gt; 1 min), return to normal activity only after 2 wk without symptoms</li> </ul>

## Late Complications of Head/Brain Injury

- seizures: 5% of head injury patients develop seizures
  - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
  - post-traumatic seizure may be immediate, early, or late
  - presence of early (within first wk) post-traumatic seizure raises incidence of late seizures
- meningitis: associated with CSF leak from nose or ear
- hydrocephalus: acute hydrocephalus or delayed normal pressure hydrocephalus (NPH)

## Spinal Cord Injury (SCI)



- see [Orthopedics](#), OR21 and [Emergency Medicine](#), ER9

## Neurogenic and Spinal Shock

1. neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by:
  - interruption of sympathetics (unopposed parasympathetics) below the level of injury
  - loss of muscle tone due to skeletal muscle paralysis below level of injury → venous pooling (relative hypovolemia)
  - blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the spinal cord injury, causing flaccid paralysis and areflexia for variable periods

## Whiplash-Associated Disorders

- definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck



### Early versus Delayed Decompression for Traumatic Cervical Spinal Cord Injury: Results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS)

*PLoS ONE* 2012;7:e32037. doi:10.1371/journal.pone.0032037

**Introduction:** This study sought to determine the relative effectiveness of early (<24 h after injury) versus late (≥24 h after injury) decompressive surgery following a traumatic cervical spinal cord injury (SCI).

**Methods/Population:** A prospective cohort study completed in 2002-2009 involving 6 North American institutions. Participants were 16-80 yr of age with a cervical SCI. Outcomes evaluated were changes in American Spinal Injury Association Impairment Scale (AIS) grade at 6 mo follow-up, complications, and mortality.

**Results:** Of 313 participants enrolled, 182 underwent early surgery and 131 underwent late surgery. 222 participants were available for follow-up at 6 mo. The odds of at least 2 grade AIS improvement were greater for those who had early surgery compared to those with late surgery (OR = 2.83, 95% CI: 1.10, 7.28). 1 mortality was observed for each group during the first 30 d post injury. No statistically significant differences were observed for complications (p = 0.21).

**Conclusion:** Early decompression surgery following a SCI is safe and associated with higher AIS improvement at 6 mo following injury.

### Initial Management of SCI

- major causes of death in SCI are aspiration and shock
- the following patients should be treated as having a SCI until proven otherwise:
  - all victims of significant trauma
  - minor trauma patients with decreased LOC or complaints of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

### Stabilization and Initial Evaluation in the Hospital

1. ABCs, immobilization (backboard/head strap), oxygenation, foley catheter to urometer, temperature regulation
2. hypotension: maintain sBP >90 mmHg with pressors (dopamine), hydration, and atropine
  - DVT prophylaxis
3. monitor CBC/electrolytes
4. focused history (see *Trauma Assessment*, NS30)
5. spine palpation: point tenderness or deformity
6. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
7. sensory level assessment: pinprick, light touch, and proprioception
8. evaluation of reflexes
9. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
10. radiographic evaluation
  - 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction
  - flexion-extension views to disclose occult instability
  - CT scan (bony injuries) typically most trauma centre use the CT as the modality of choice for looking at fractures, very sensitive with the high resolution scanners.
  - MRI mandatory if neurological deficits (soft tissue injuries)

### Medical Management Specific to SCI

- option: methylprednisolone (given within 8 h of injury) this is controversial and you need to confer with Neurosurgery service
- $\pm$  decompression in acute, non-penetrating SCI



**Pharmacological Therapy for Acute Spinal Cord Injury: Congress of Neurological Surgeons (CNS) and American Association of Neurological Surgeons (AANS) Guidelines**

*Neurosurgery* 2013;72(Suppl 2):93-105

Level I Recommendations

- No Class I or Class II medical evidence supports the use of methylprednisone in the treatment of acute SCI. Several Class II and Class III studies have been published stating inconsistent effects of methylprednisone likely related to random chance or selection bias.
- Administration of GM-1 ganglioside (Sygen) for the treatment of acute SCI is not recommended.

## Fractures of the Spine

### FRACTURES AND FRACTURE-DISLOCATIONS OF THE THORACIC AND LUMBAR SPINE

- assess ligamentous instability using flexion/extension x-ray views of C-spine  $\pm$  MRI
- thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
  - anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
  - middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
  - posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous and ligamentum ligaments

### Types of Injury (Denis Classification)

- **compression fracture** (58%)
  - produced by flexion
  - posterior ligament complex (supraspinous and interspinous ligaments, ligamentum flavum and intervertebral joint capsules) remain intact
  - fractures are stable but lead to kyphotic deformity
- **burst fracture** (17%)
  - stable: anterior and middle columns parted with bone retropulsed nearby
    - ♦ hallmark is pedicle widening on AP X-ray
    - ♦ spinal cord (seen on x-ray and CT); posterior column is uninjured
  - unstable: same as the stable but with posterior column disruption (usually ligamentous)
- **flexion distraction injury** (6%)
  - hyperflexion and distraction of posterior elements
    - ♦ middle and posterior columns fail in distraction
  - classic: Chance = horizontal fracture through posterior arch, pedicles, posterior vertebral body
  - can be purely ligamentous, i.e. through PLL and disc
- **fracture-dislocation** (6%)
  - anterior and cranial dislocation of superior vertebral body  $\rightarrow$  3 column failure
  - three types:
    - ♦ flexion-rotation
    - ♦ flexion-distraction
    - ♦ shear/hyperextension (rare)

### Management of Thoracolumbar Injury

- severity and management based on TLICS classification (see sidebar)



#### TLICS Scoring

Parameter	Points
Morphology	
Compression fracture	1
Burst fracture	2
Translational/rotational fracture	3
Distraction	4
Neurologic status	
Intact	0
Nerve root injury	2
Spinal cord status	
Incomplete	3
Complete	2
Cauda equine	3
Posterior ligamentous complex	
Intact	0
Injury suspected/indeterminate	2
Injured	3

- TLICS scoring based on morphology of injury, status of posterior ligamentous complex, and neurological status
- Non-operative management if TLICS = 0-3, operative management if TLICS = 5+, either operative or non-operative if TLICS = 4

## FRACTURES OF THE CERVICAL SPINE

### Types of Injury

- C1 vertebral fracture (Jefferson fracture)
  - vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing the lateral masses of the atlas outward and disrupting the ring of the atlas
  - also can cause an occipital condylar fracture
- odontoid process fracture (see Figure 26)
  - causes C1 and odontoid of C2 to move independently of C2 body
  - this occurs because
    - ♦ normally C1 vertebra and odontoid of C2 are a single functional unit
    - ♦ alar and transverse ligaments on posterior aspect of odontoid most commonly remain intact following injury
  - patients often report a feeling of instability and present holding their head with their hands
- C2 vertebral fracture (hangman fracture, traumatic spondylolisthesis of axis):
  - bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3
  - usually neurologically intact
- Clay-Shoveler fracture
  - avulsion of spinous process, usually C6 or C7

### Imaging

- AP spine x-ray (open-mouth and lateral view), CT

### Treatment

- immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
- Type II and III odontoid fractures
  - consider surgical fixation for comminution, displacement or inability to maintain alignment with external immobilization
  - confirm stability after recovery with flexion-extension x-rays

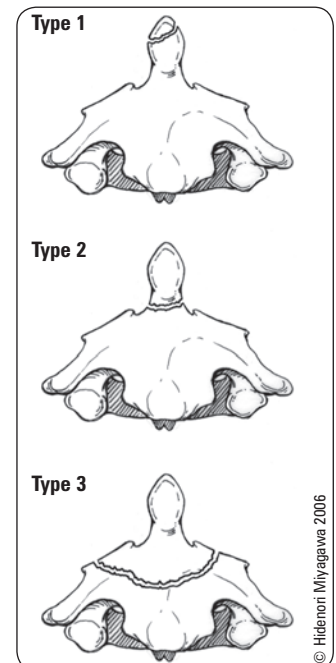


Figure 26. Odontoid fracture classification



## Neurologically Determined Death

### Definition

- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascular activity may persist for up to 2 wk

### Criteria of Diagnosis

- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature  $>32^{\circ}\text{C}$ , no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes:
  - absent pupillary light reflex
  - absent corneal reflexes
  - absent oculocephalic response
  - absent caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides)
  - absent pharyngeal and tracheal reflexes
  - absent cough with tracheal suctioning
  - absent respiratory drive at  $\text{PaCO}_2 >60$  mmHg or  $>20$  mmHg above baseline (apnea test)
- 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
- confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

## Coma

### Definition

- an unrousable state in which patients show no meaningful response to environmental stimuli

### Pathophysiology

- lesions affecting the cerebral cortex bilaterally, the reticular activating system (RAS) or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

**Classification**

- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B<sub>12</sub>)
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
  - infections (meningitis, encephalitis)
  - trauma (concussion, diffuse shear axonal damage)

**Investigations and Management**

- ABCs
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP, EEG

## Persistent Vegetative State

**Definition**

- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- “awake but not aware”
- follows comatose state

**Etiology/Prognosis**

- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

## Pediatric Neurosurgery

### Spinal Dysraphism

**SPINA BIFIDA OCCULTA****Definition**

- congenital absence of a spinous process and a variable amount of lamina
- no visible exposure of meninges or neural tissue

**Epidemiology**

- 15-20% of the general population; most common at L5 or S1

**Etiology**

- failure of fusion of the posterior neural arch

**Clinical Features**

- no obvious clinical signs
- presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia)

**Investigations**

- plain film: absence of the spinous process along with minor amounts of the neural arch
- U/S, MRI to exclude spinal anomalies

**Treatment**

- requires no treatment

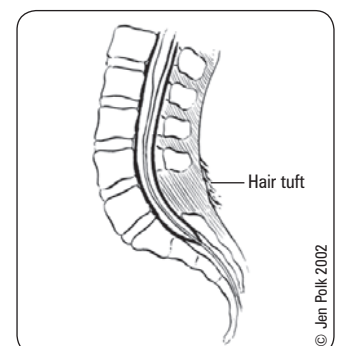


Figure 27. Spina bifida occulta

## MENINGOCELE (SPINA BIFIDA APERTA)

### Definition

- herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue

### Etiology

- primary failure of neural tube closure

### Clinical Features

- most common in lumbosacral area
- usually no disability, low incidence of associated anomalies and hydrocephalus

### Investigations

- plain films, CT, MRI, U/S, echo, genitourinary (GU) investigations

### Treatment

- surgical excision and tissue repair (excellent results)

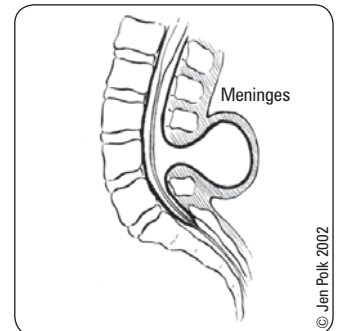


Figure 28. Meningocele

## MYELOMENINGOCELE (SPINA BIFIDA APERTA)

### Definition

- herniation of meningeal and CNS tissue through a defect in the spine

### Etiology

- same as meningocele

### Clinical Features

- sensory and motor changes distal to anatomic level producing varying degrees of weakness
- urinary and fecal incontinence
- 65-85% of patients with myelomeningocele have hydrocephalus
- most have Type II Chiari malformation (see *Chiari Malformations*, NS37)

### Investigations

- plain films, CT, MRI, U/S, echo, GU investigations

### Treatment

- surgical closure to preserve neurologic status and prevent CNS infections
- closure in-utero shown to decrease hydrocephalus and improve post natal motor scores

### Prognosis

- operative mortality close to 0%, 95% 2-yr survival
- 80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence
- early mortality usually due to Chiari malformation complications (respiratory arrest and aspiration), whereas late mortality is due to shunt malfunction

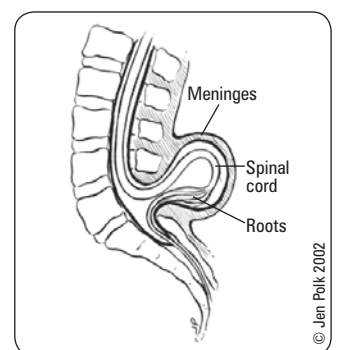


Figure 29. Myelomeningocele

## Intraventricular Hemorrhage (IVH)

- see [Pediatrics](#), P73



## Hydrocephalus in Pediatrics

### Etiology

- congenital
  - aqueductal anomalies, primary aqueductal stenosis in infancy
  - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  - Dandy-Walker malformation (2-4%)
  - Chiari malformation, especially Type II
  - myelomeningocele
- acquired
  - post meningitis
  - post hemorrhage (SAH, IVH)
  - masses (vascular malformation, neoplastic)

### Clinical Features

- symptoms and signs of hydrocephalus are age related in pediatrics
- increased head circumference (HC), bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding and vomiting
- “cracked pot” sound on cranial percussion



- scalp vein dilation (increased collateral venous drainage)
- sunset sign – forced downward deviation of eyes
- episodic bradycardia and apnea

#### Investigations

- skull x-ray, U/S, CT, MRI, ICP monitoring

#### Treatment

- similar to adults (see *Hydrocephalus*, NS8)

## Dandy-Walker Malformation

#### Definition

- atresia of foramina of Magendie and Luschka, resulting in:
  - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic cerebellar hemispheres
  - posterior fossa cyst, enlarged posterior fossa
  - dilatation of 4th ventricle (also 3rd and lateral ventricles)
- associated anomalies
  - hydrocephalus (90%)
  - agenesis of corpus callosum (17%)
  - occipital encephalocele (7%)

#### Epidemiology

- 2-4% of pediatric hydrocephalus

#### Clinical Features

- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

#### Investigations

- ultrasound, CT, MRI

#### Treatment

- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
  - e.g. ventriculoperitoneal (VP) shunt, cystoperitoneal (CP) shunt, limboperitoneal (LP) shunt, ventriculoatrial (VA) shunt, lumbar drain

#### Prognosis

- 75-100% survival, 50% have normal IQ

## Chiari Malformations

#### Definition

- malformations at the medullary-spinal junction

#### Etiology

- unclear, likely maldevelopment/dysgenesis during fetal life

#### Categories

- Type I (cerebellar ectopia)
  - definition: cerebellar tonsils lie below the level of the foramen magnum
  - epidemiology: average age at presentation 15 yr
  - clinical features:
    - ♦ many are asymptomatic
    - ♦ scoliosis
    - ♦ brain compression
    - ♦ central cord syndrome (65%)
    - ♦ syringomyelia (50%)
    - ♦ foramen magnum compression syndrome (22%)
    - ♦ cerebellar syndrome (11%)
    - ♦ hydrocephalus (10%)
- Type II
  - definition: part of cerebellar vermis, medulla, and 4th ventricle extend through the foramen magnum often to midcervical region
  - almost always associated with a myelomeningocele
  - epidemiology: present in infancy
  - clinical features: findings due to brainstem and lower cranial nerve dysfunction
  - syringomyelia, hydrocephalus in >80%

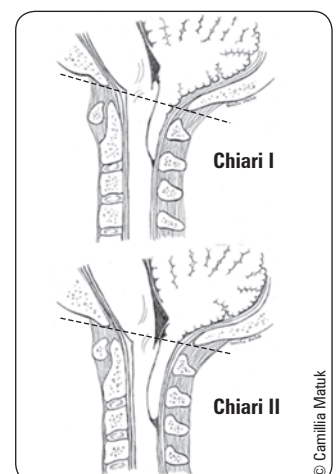


Figure 30. Chiari malformations

**Investigations**

- MRI

**Treatment**

- indications for surgical decompression
  - Type I: symptomatic patients (early surgery recommended; <2 yr post symptom onset) → suboccipital craniectomy, duraplasty
  - Type II: neurogenic dysphagia, stridor, apneic spells → cervical laminectomy, duraplasty

## Craniosynostosis

**Definition**

- premature closure of the cranial suture(s)

**Classification**

- sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
- coronal: expansion in superior and lateral direction (brachiocephaly)
- metopic (trigonocephaly)
- lambdoid: least common

**Epidemiology**

- 0.6/1000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

**Clinical Features**

- skull deformity, raised ICP ± hydrocephalus
- ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
- must differentiate between positional plagiocephaly (secondary to back sleeping)

**Investigations**

- plain radiographs, CT scan

**Treatment**

- parental counseling about nature of deformity, associated neurological symptoms
- surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

## Pediatric Brain Tumours

- see also *Tumours*, NS10

**Epidemiology**

- 20% of all pediatric cancers (second only to leukemia)
- 60% of pediatric brain tumours are infratentorial
- pediatric brain tumours arise from various cellular lineages
  - glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see *Astrocytoma*, NS13 for details)
  - primitive nerve cells: supratentorial [primitive neuroectodermal tumour (PNET)]
    - ♦ 90% of neonatal brain tumours, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
  - non-neuronal cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma (schwannoma), pituitary adenoma, others

**Clinical Features**

- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escapes diagnosis due to expansile cranium and neural plasticity in children

**Table 17. Overview of Childhood Primary Brain Tumours**

<b>Pilocytic (low grade) Astrocytoma</b>	<ul style="list-style-type: none"> <li>• Usually in posterior fossa</li> <li>• Well circumscribed</li> <li>• Benign, good prognosis</li> </ul>
<b>Medulloblastoma</b>	<ul style="list-style-type: none"> <li>• A primitive neuroectodermal tumour (PNET)</li> <li>• In cerebellum → compresses 4th ventricle → hydrocephalus</li> <li>• Highly malignant</li> </ul>
<b>Ependymoma</b>	<ul style="list-style-type: none"> <li>• In 4th ventricle → hydrocephalus</li> <li>• Poor prognosis</li> </ul>
<b>Hemangioblastoma</b>	<ul style="list-style-type: none"> <li>• Often cerebellar</li> <li>• Associated with von Hippel-Lindau syndrome with retinal angiomas</li> <li>• Can produce EPO → secondary polycythemia</li> </ul>
<b>Craniopharyngioma</b>	<ul style="list-style-type: none"> <li>• Causes bitemporal hemianopsia (thus often confused with pituitary adenoma)</li> <li>• Most common supratentorial childhood tumour</li> <li>• Benign</li> </ul>

**Relative Frequency of Pediatric Brain Tumours**

Tumour Type	Percent (%)
Astrocytoma, low-grade	40
Supratentorial	(23)
Infratentorial	(17)
Medulloblastoma	20
Brainstem glioma	8
Ependymoma	8
Malignant glioma	6
Craniopharyngioma	6
PNET	4
Pineal, germ cell tumour	3
Other	5

Reprinted with permission from Elsevier.  
 Kun LE. Brain tumours: Challenges and directions.  
*Pediatric Clin of Nor Am* 1997;44:907-17

# Functional Neurosurgery

## Movement Disorders

- see *Tremor, Parkinson's Disease, Dystonia, and Multiple Sclerosis* sections in [Neurology](#), N25, N26, N27, N46, respectively



**Table 18. Surgical Targets for Movement Disorders**

Disorder	Indications	Procedures	Outcomes	Morbidity
<b>Parkinson's Disease</b>	Intractable contralateral bradykinesia/tremor Failure of medical management (advanced disease) Drug-induced dyskinesias (see dystonia, below)	Simultaneous, bilateral surgery/stimulation is most common Preferred target: anterodorsal subthalamic nucleus (STN) Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus pars interna (GPI) Caudal zona incerta Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus	39-48% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores Reduced dosage of medications (STN) More effective than medical management in advanced PD Early intervention may reduce severity, course, and progression of disease Of little benefit for patients with atypical presentations	Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias Involuntary movements Cognitive functioning: decreased lexical fluency, impaired executive function (STN > GPI) Psychiatric: depression, mania, anxiety, apathy (STN > GPI)
<b>Dystonia</b>	Contralateral primary (generalized) dystonias; cervical and tardive dystonias (GPI) Contralateral secondary dyskinesia (i.e. drug-induced: L-dopa, neuroleptics; STN)	Preferred target (primary dystonia): stereotactic ablation (pallidotomy)/stimulation of posteroventral GPI Secondary dystonia: stimulation of anterodorsal STN Stimulation of ventral posterior lateral (VPL) thalamic nucleus	Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDs) score Secondary dystonia: 62-89% improvement in dystonias Delayed effects: weeks → months	Intracerebral hemorrhage, infection, seizure (1%-4%) Minor effects on cognitive functioning (especially decreased lexical fluency; STN > GPI)
<b>Tremor</b>	Contralateral appendicular ET (first disorder to be treated by DBS; DBS is viable alternative to Rx) Intention tremor (IT) resulting from demyelination of cerebellar outflow tracts (e.g. in multiple sclerosis) Brainstem tremor (Holmes tremor)	Preferred target: stereotactic ablation (thalamotomy)/stimulation of Vim nucleus of thalamus Other targets: stimulation of caudal zona incerta Parkinsonian tremor: stimulation of anterodorsal STN	Durable reductions in essential tremor rating scale (ETRS) scores Reduced dosage of medications Conflicting data on vocal/facial tremor	Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias/pain Dysarthria Ataxia Minor effects on cognitive functioning (especially decreased lexical fluency) Tolerance may develop over time

## Neuropsychiatric Disorders

- see *Tourette's Syndrome, Obsessive Compulsive Disorder and Depression* sections in [Neurology](#), N28 and [Psychiatry](#), PS16, PS10



**Table 19. Surgical Targets for Neuropsychiatric Disorders**

Disorder	Indications	Procedures	Outcomes	Morbidity
<b>Obsessive Compulsive Disorder (OCD)</b>	Severe symptoms refractory to medical management	Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC)	Currently under investigation Reportedly 25-75% response rate	Intracerebral hemorrhages (1%-2%) Mild effects on cognitive functioning Anxiety ± panic disorder (case report)
<b>Tourette's Syndrome</b>	Severe symptoms refractory to medical management	Stimulation of midline intralaminar nuclei of the thalamus Stimulation of motor and limbic portions of GPI Stimulation of the anterior limb of the IC	Currently under investigation Reportedly >70% reduction in vocal or motor tics + urge	Intracerebral hemorrhages (1%-2%) Mild sexual dysfunction
<b>Major Depressive Disorder (MDD)</b>	Severe depression refractory to medical management and ECT	Stimulation of the subgenual cingulate cortex	Currently under investigation Reportedly 60% response rate; 35% remission rate	Intracerebral hemorrhages (1%-2%) Pain, headache Worsening mood, irritability

## Chronic Pain

**Table 20. Surgical Targets for Chronic Pain**

Disorder	Indications	Procedures	Outcomes	Morbidity
<b>Neuropathic Pain</b>	Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, complex regional pain syndrome)	Preferred target: stimulation of the contralateral VPL VPM thalamic nuclei $\pm$ periventricular/periaqueductal grey matter (PVG/PAG) Other targets: stimulation of the contralateral IC Stimulation of the contralateral motor cortex	47% improvement in perception of pain intensity Less favourable results in central pain syndromes and poorly localized pain	Intracerebral hemorrhages (1%-2%) Paraesthesia Anxiety $\pm$ panic disorder
<b>Nociceptive Pain</b>	Severe, intractable, organic nociceptive pain	Bilateral (most common) stimulation of the PVG/PAG	Reportedly 63% improvement in perception of pain intensity	Intracerebral hemorrhages (1%-2%) Paraesthesia Anxiety $\pm$ panic disorder

## Surgical Management of Epilepsy

- see [Neurology](#), N16 for the medical treatment of epilepsy

### Indications

- medically refractory seizures, usually defined as seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing. Other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

### Procedure

- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common

### Outcomes

- 41-79% of adult patients are seizure free for 5 yr after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

### Morbidity

- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anteromedial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 yr

### Predictors

- positive predictive factors for seizure freedom following anteromedial temporal lobectomy
  - hippocampal sclerosis (unilateral)
  - focal localization of interictal epileptiform discharges
  - absence of preoperative generalized seizures
  - tumoural cause
  - complete resection of the lesion



#### A Randomized, Controlled Trial of Surgery for Temporal Lobe Epilepsy

*NEJM* 2001;345:311-318

**Introduction:** This RCT evaluates the efficacy and safety of neurosurgery for temporal lobe epilepsy.

**Methods:** 80 patients with poorly controlled temporal lobe epilepsy were randomized for surgery (n=40) or for continued treatment with antiepileptic drugs (n=40). The primary outcome was freedom from seizures that impair awareness of self and surroundings during the period of 1 yr. Secondary outcomes included frequency and severity of seizures, quality of life, disability and death.

**Results:** The surgical group had higher cumulative proportion of patients without seizures impairing awareness compared to the medical group (p<0.01). The surgical group also had lower seizure frequency (p<0.001) and better quality of life (p<0.001). 4 patients in the surgical group had adverse effects (thalamic infarct, n = 1; wound infection, n = 1; verbal memory decline impairment occupation, n = 2). One patient in the medical group died; no patients died in the surgical group.

**Conclusions:** In patients with poorly controlled temporal-lobe epilepsy, surgery is superior to prolonged medical therapy.

## Surgical Management for Trigeminal Neuralgia

- reserved for cases refractory to medical management; see [Neurology](#), N36 for medical management



### Surgical Options

- trigeminal nerve branch procedures
  - local blocks (phenol, alcohol)
  - neurectomy of the trigeminal branch
- nerve branches
  - V<sub>1</sub> block at the supraorbital, supratrochlear nerves
  - V<sub>2</sub> block at the foramen rotundum or infraorbital nerves
  - V<sub>3</sub> block at the foramen ovale
- percutaneous trigeminal rhizotomy
  - glycerol injection
  - mechanotrauma via catheter balloon
- radiofrequency thermocoagulation
- Gamma Knife® radiosurgery
- microvascular decompression
  - posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable Teflon® felt

## Common Medications

Table 21. Common Medications

Drug Name	Dosing Schedule	Indications	Side Effects	Common Interactions	Contraindications	Comments
<b>lorazepam</b> (Ativan®)	4 mg IV over 2 min, q10-15min (do not exceed 8 mg/12h)	Status epilepticus	Drowsiness, sedation	Other CNS depressants, digoxin (increases digoxin levels)		Start phenytoin loading simultaneously
<b>carbamazepine</b> (Tegretol®)	Trigeminal neuralgia (tic douloureux): 100 mg PO bid, increase by 200 mg/d up to a maximum of 1200 mg/d Seizures: 200 mg PO bid, increase by 200 mg (inpatient: q3d; outpatient: q7d) until therapeutic level achieved (usual optimum dosage: 800-1200 mg/d; range: 600-2000 mg/d)	Trigeminal neuralgia Seizures	Worsening of seizures, heart failure, arrhythmias, AV block, aplastic anemia, agranulocytosis, thrombocytopenia, hepatitis, erythema multiforme, Stevens-Johnson syndrome	Lithium (increases lithium toxicity), MAOI Other meds may increase carbamazepine levels or have decreased effects	Hypersensitivity to TCAs, previous bone marrow suppression, MAOI in past 14 d	Monitor CBC (potential hematological toxicity)
<b>phenytoin</b> (Dilantin®)	Seizures: Loading dose: 18 mg/kg slow IV or 300-600 mg PO/d divided bid/tid Maintenance: 200-500 mg IV/d (max rate: <40-50 mg/min or 300 mg PO q4h); average maintenance dose: 300 mg/d PO Status epilepticus: 200 mg IV over 30 min (~20 mg/kg; if not taking regularly), or 500 mg IV over 10 min (if already on phenytoin)	Seizures Status epilepticus	Thrombocytopenia, leukopenia, heart failure, agranulocytosis, pancytopenia, toxic hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis	Other meds may increase phenytoin levels and toxicity or have decreased effects	Bradycardias, heart block	Important to give over time to prevent causing a cardiac arrest
<b>dexamethasone</b> (Decadron®)	Loading dose: 10-20 mg IV Maintenance: 4-6 mg IV/d divided qid (may be PO)	Cerebral edema (e.g. secondary to tumour, head injury, pseudotumour cerebri) Preoperative preparation for patients with increased ICP secondary to brain neoplasms	Pseudotumour cerebri, seizures, leukopenia, heart failure, arrhythmias, thromboembolism, pancreatitis, acute adrenal insufficiency; avoid abrupt withdrawal	Aminoglutethimide, antidiabetics, ASA, NSAIDs, barbiturates, phenytoin, rifampin, cardiac glycosides, cyclosporine, ephedrine, oral anticoagulants, potassium-depleting drugs, salicylates, skin-testing antigens, toxoids, vaccines	Systemic fungal infections, immunosuppressive dose with live virus vaccines	No longer used in acute spinal cord injury

**Table 21. Common Medications** (continued)

Drug Name	Dosing Schedule	Indications	Side Effects	Common Interactions	Contraindications	Comments
<b>mannitol</b>	1-1.5 g/kg IV rapid infusion (350 mL of 20% solution) followed by 0.25 g/kg IV q6h	Raised ICP	Seizures, heart failure	Lithium (increases excretion of lithium)	Anuria, severe pulmonary congestion, frank pulmonary edema, severe heart failure, severe dehydration, metabolic edema, progressive renal disease or dysfunction, active intracranial bleeding except during craniotomy	Effect occurs in 1-5 min, maximal at 20-60 min Often alternated with furosemide 10-20 mg IV q6h Indwelling urinary catheter to measure ins and outs
<b>nimodipine (Nimotop®)</b>	60 mg PO/NG q4h x 21 d started within 96 h of SAH	Vasospasm in SAH	Decreased blood pressure, tachycardia, dyspnea	Antihypertensives (may increase hypotensive effects), CCB (may increase effects), cimetidine (increases nimodipine bioavailability)	None known	Causes vasodilation Only calcium channel blocker that crosses blood brain barrier Use half the normal dose for liver failure; monitor BP always

## References

### Textbooks

- Walton JGR, Hutchinson M, McArdle MJF, O'Brien MD, Thomas PK, Willison RG. *Aids to the examination of the peripheral nervous system*. London: Bailliere Tindall, 1986.
- Crossman AR, Neary D. *Neuroanatomy: an illustrated colour text*. Toronto: Churchill Livingstone, 1998.
- Fitzgerald MJT. *Neuroanatomy: basic and clinical*, 3rd ed. Philadelphia: WB Saunders, 1997.
- Goetz CG, Pappert EJ. *Textbook of clinical neurology*, 1st ed. Toronto: WB Saunders, 1999.
- Greenberg MS. *Handbook of neurosurgery*, 5th ed. New York: Thieme, 2001.
- Guy M, McKhann, Guy McKhann II, Neil Kitchen. *Clinical neurology and neurosurgery*. Theme Medical Publishers, 2003.
- Lindsay KW, Bone I. *Neurology and neurosurgery illustrated*. New York: Churchill Livingstone, 2004.
- Nieuwenhuys R, Voogd J, van Huijzen C. *The human central nervous system*, 3rd ed. New York: Springer-Verlag, 1988.
- Nursing 2004 Drug Handbook, 24th ed. New York: Springhouse Lippincott Williams & Wilkins, 2004.

### Journal Articles

- Adzick N, Thom E, Spong C, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. *NEJM* 2011;364:993-1004.
- Ahn NU, Ahn UM, Nallamshetty L, et al. Cauda equina syndrome in ankylosing spondylitis (the CES-AS syndrome): meta-analysis of outcomes after medical and surgical treatments. *J Spinal Disord* 2001;14:427-433.
- Ross J, Al-Shahi Salman R. Interventions for treating brain arteriovenous malformations in adults. *Cochrane DB Syst Rev* 2010;7:CD003436.
- Barker FG 2nd, Ogilvy CS. Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. *J Neurosurg* 1996;84:405-414.
- Barnett H, Taylor W, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. *NEJM* 1998;339:1415-1425.
- Bracken MB, Shepard MJ, Holford TR, et al. Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. *J Neurosurg* 1998;89:699-706.
- Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *NEJM* 2012;367:2471-2481.
- Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane DB Syst Rev* 2007;3:CD000277.
- Eidlow J, Caplan L. Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *NEJM* 2000;342:29-36.
- el Barzouhi A, Vleggeert-Lankamp CL, Lycklama à Nijeholt GJ, et al. Magnetic resonance imaging in follow-up assessment of sciatica. *NEJM* 2013;368:999-1007.
- Executive Committee for the Asymptomatic Carotid Atherosclerosis Study (ACAS). Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421-1428.
- Fehlings MG, Tator CH. An evidence-based review of surgical decompression for acute spinal cord injury: rationale, indications, and timing based on experimental and clinical studies. *J Neurosurg* 1999;91(1 Suppl):1-11.
- Fehlings MG, Vaccaro A, Wilson JR, et al. (2012) Early versus delayed decompression for traumatic cervical spinal cord injury: results of the surgical timing in acute spinal cord injury study (STASCIS). *PLoS ONE* 7:e32037. doi:10.1371/journal.pone.0032037.
- Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D, MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491-2502.
- Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. *Neurosurgery* 2013;72(Suppl 2):93-105.
- International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms – risk of rupture and risks of surgical intervention. *NEJM* 1998;339:1725-1733.
- Kun, LE. Brain Tumours: challenges and directions. *Pediat Clin N Am* 1997;44:907-917.
- Mark DG, Hung YY, Offerman SR, et al. Nontraumatic subarachnoid hemorrhage in the setting of negative cranial computed tomography results: external validation of a clinical and imaging prediction rule. *Ann Emerg Med* 2012;pii:S0196-0644:1508-1509.
- Mintz A, Perry J, Spithoff K, et al. Management of single brain metastasis: a practice guideline. *Curr Oncol* 2007;14:131-143.
- Molyneux AJ, Kerr RS, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol* 2009;8:427-433.
- MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491-1502.
- Ogilvy CS, Stieg PE, Awad I, et al. Recommendations for the management of intracranial arteriovenous malformations. *Circulation* 2001;103:2644-2657.
- Portenoy RK, Lipton RB, Foley KM. Back pain in the cancer patient: an algorithm for evaluation and management. *Neurology* 1987;37:134-138.
- Porter PJ, Willinsky RA, Harper W, et al. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *J Neurosurg* 1997;87:190-197.
- Saal JS, Saal JA, Yurth EF. Nonoperative management of hemiated cervical intervertebral disc with radiculopathy. *Spine* 1996;21:1877-1883.
- Sayer FT, Kronwall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. *Spine* 2006;6:335-343.
- Shapiro S. Medical realities of cauda equina syndrome secondary to lumbar disc herniation. *Spine* 2000;25:348-351.
- Shemie S, Doig C, Dickens B, et al. Severe brain injury to neurological determination of death: canadian forum recommendations. *CMAJ* 2006;174:S1-30.
- Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. *Lancet Neurol* 2008;7:525-37.
- Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg* 1986;65:476-83.
- Stiell IG, Wells GA, Vandemheen K, et al. The Canadian CT head rule for patients with minor head injury. *Lancet* 2001;357:1391-1396.
- The North American Symptomatic Carotid Endarterectomy Trial (NASCET). Beneficial effects of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *NEJM* 1991;325:445-453.
- Tseng JH, Tseng MY. Brain abscess in 142 patients: factors influencing outcome and mortality. *Surg Neurol* 2006;65:557-562.
- Wiebe S, Blume WT, Girvin JP, et al. Effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *NEJM* 2001;345:311-318.



Rebecca Ronsley, Jamie Saperia and Alia Sunderji, chapter editors

Jieun Kim and Daniel Soong, associate editors

Jeff Martin, EBM editor

Dr. Filomena Meffe, Dr. Eva Mocarski and Dr. Amanda Selk, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Normal Labour and Delivery</b> . . . . .	<b>31</b>
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	Definition of Labour	
<b>Pregnancy</b> . . . . .	<b>2</b>	The Cervix	
Diagnosis of Pregnancy		The Fetus	
Maternal Physiology		Four Stages of Labour	
<b>Prenatal Care</b> . . . . .	<b>4</b>	The Cardinal Movements of the Fetus during Delivery	
Preconception Counselling		Analgesic and Anesthetic Techniques in Labour and Birth	
Initial Prenatal Visit		Fetal Monitoring in Labour	
Subsequent Prenatal Visits		<b>Induction of Labour</b> . . . . .	<b>36</b>
Prenatal Screening and Diagnostic Tests		Induction Methods	
<b>Counselling of the Pregnant Woman</b> . . . . .	<b>9</b>	Augmentation of Labour	
Nutrition		<b>High Risk Labour and Delivery</b> . . . . .	<b>38</b>
Lifestyle		Preterm Labour	
Medications		Premature Rupture of Membranes	
Immunizations		Breech Presentation	
Radiation		Vaginal Birth After Cesarean (VBAC) aka Trial of Labour After Cesarean (TOLAC)	
<b>Termination of Pregnancy</b> . . . . .	<b>11</b>	Prolonged Pregnancy	
<b>Prenatal Fetal Monitoring</b> . . . . .	<b>12</b>	Intrauterine Fetal Death	
Fetal Movements		<b>Complications of Labour and Delivery</b> . . . . .	<b>42</b>
<b>Medical Conditions in Pregnancy</b> . . . . .	<b>13</b>	Meconium in Amniotic Fluid	
Iron and Folate Deficiency Anemia		Abnormal Progression of Labour (Dystocia)	
Diabetes Mellitus (DM)		Shoulder Dystocia	
Hypertension in Pregnancy		Umbilical Cord Prolapse	
Nausea and Vomiting		Uterine Rupture	
Hyperemesis Gravidarum		Amniotic Fluid Embolus	
Jaundice in Pregnancy		Chorioamnionitis	
Urinary Tract Infection (UTI)		<b>Operative Obstetrics</b> . . . . .	<b>46</b>
Infections During Pregnancy		Operative Vaginal Delivery	
Venous Thromboembolism (VTE)		Forceps	
<b>Bleeding in Pregnancy</b> . . . . .	<b>22</b>	Vacuum Extraction	
First and Second Trimester Bleeding		Lacerations	
Spontaneous Abortions		Episiotomy	
<b>Ectopic Pregnancy</b> . . . . .	<b>23</b>	Cesarean Delivery	
<b>Antepartum Hemorrhage</b> . . . . .	<b>25</b>	<b>Puerperal Complications</b> . . . . .	<b>48</b>
Placenta Previa		Postpartum Hemorrhage	
Abruptio Placentae		Retained Placenta	
Vasa Previa		Uterine Inversion	
<b>Multiple Gestation</b> . . . . .	<b>28</b>	Postpartum Pyrexia	
Twin-Twin Transfusion Syndrome		Mastitis	
<b>Growth Discrepancies</b> . . . . .	<b>29</b>	Postpartum Mood Alterations	
Intra-Uterine Growth Restriction		<b>Postpartum Care</b> . . . . .	<b>52</b>
Macrosomia		Breastfeeding and Drugs	
Polyhydramnios/Oligohydramnios		<b>Common Medications</b> . . . . .	<b>53</b>
		<b>References</b> . . . . .	<b>54</b>

## Basic Anatomy Review

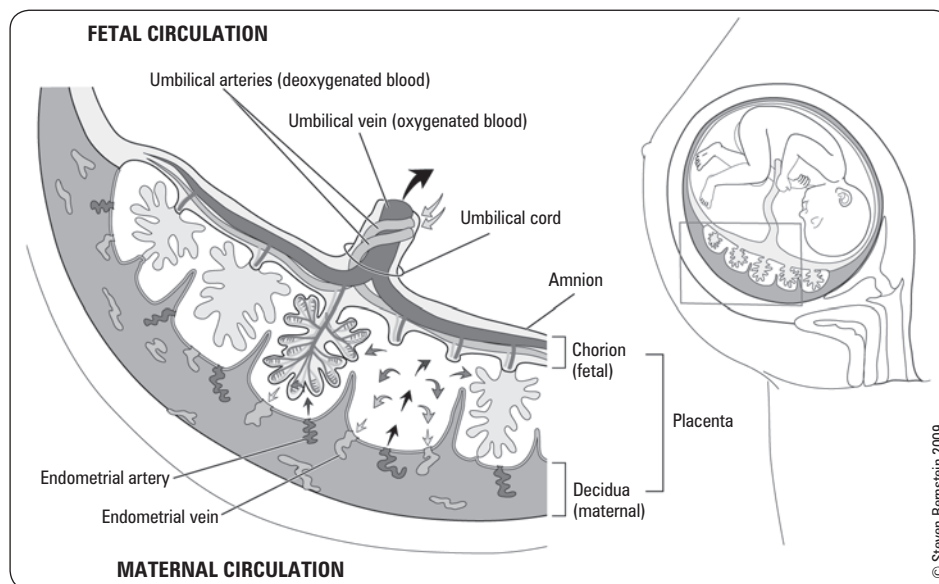


Figure 1. Placental blood flow

### Placenta

- site of fetal nutritive, respiratory, and excretory function
- discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- produces hormones such as progesterone, placental lactogen, estrogen, relaxin,  $\beta$ -hCG and IGFs
- poor implantation can lead to spontaneous abortion
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see *Antepartum Hemorrhage*, OB25)

## Pregnancy



### Diagnosis of Pregnancy

#### History

- obstetrical and gynecological history
- obtain the year, location, mode of delivery, duration of labour, sex, gestational age, birth weight and complications of every pregnancy; organize into **GTPAL** format:
  - **G** (Gravidity)
    - ♦ **G**: total number of pregnancies of any gestation
    - ♦ includes current pregnancy, abortions, ectopic pregnancies, and hydatidiform moles (multiple gestation = one pregnancy)
  - **P** (Parity) (TPAL)
    - ♦ **T**: number of term infants delivered (>37 wk)
    - ♦ **P**: number of premature infants delivered (20-36+6 wk)
    - ♦ **A**: number of abortions (loss of intrauterine pregnancy prior to viability of fetus <20 wk and/or <500 g fetal weight)
      - induced (therapeutic) and spontaneous (miscarriage)
    - ♦ **L**: number of living children
- symptoms: amenorrhea, nausea and/or vomiting, breast tenderness, urinary frequency, fatigue

#### Physical Signs

- Goodell's sign: softening of the cervix (4-6 wk)
- Chadwick's sign: bluish discolouration of the cervix and vagina due to pelvic vasculature engorgement (6 wk)
- Hegar's sign: softening of the cervical isthmus (6-8 wk)
- uterine enlargement
- breast engorgement

## Acronyms

AC	abdominal circumference
ACOG	American Congress of Obstetricians and Gynecologists
AFI	amniotic fluid index
AFLP	acute fatty liver of pregnancy
AFV	amniotic fluid volume
ALPHA	antenatal psychosocial health assessment
AP	anteroposterior
APS	antiphospholipid antibody syndrome
BPP	biophysical profile
C/S	Cesarean section
CPD	cephalopelvic disproportion
CTG	cardiotocography
CVS	chorionic villus sampling
D&C	dilatation and curettage
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
ECV	external cephalic version
EDC	estimated date of confinement
EFM	electronic fetal monitoring
EFW	estimated fetal weight
FDP	fibrin degradation products
FHR	fetal heart rate
FL	femur length
FM	fetal movement
FPG	fasting plasma glucose
FTS	first trimester screen
GA	gestational age
GBS	Group B <i>Streptococcus</i>
GDM	gestational diabetes mellitus
HC	head circumference
HELLP	hemolysis, elevated liver enzymes, low platelets
IGF	infant growth factors
IMM	intramymetrial
IOL	induction of labour
IPS	integrated prenatal screen
IUFD	intrauterine fetal death
IUGR	intrauterine growth restriction
IVH	intraventricular hemorrhage
LLDP	left lateral decubitus position
LMP	last menstrual period
MSAFP	maternal serum $\alpha$ -fetoprotein
MSS	maternal serum screen
MTX	methotrexate
NST	non-stress test
NTDs	neural tube defects
NTUS	nuchal translucency ultrasound
OA	occiput anterior
OGCT	oral glucose challenge test
oNTD	open neural tube defect
OP	occiput posterior
OT	occiput transverse
PAPP-a	pregnancy-associated plasma protein a
PG	plasma glucose
PPD	postpartum depression
PPH	postpartum hemorrhage
PPROM	preterm premature rupture of membranes
PROM	premature rupture of membranes
PTL	preterm labour
RDS	respiratory distress syndrome
ROM	rupture of membranes
SFH	symphysis fundal height
SOCG	Society of Obstetricians and Gynaecologists of Canada
SVD	spontaneous vaginal delivery
TENS	transcutaneous electrical neuro stimulation
TPN	total parental nutrition
UTI	urinary tract infection
VBAC	vaginal birth after Cesarean



#### Umbilical Vessels

Always check the umbilical cord for 2 arteries and 1 vein: approximately 1/3 of babies with a single uterine artery will have another anomaly.

## Investigations

- **β-hCG:** peptide hormone composed of α and β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy
  - positive in serum 9 d post-conception, positive in urine 28 d after first day of LMP
  - plasma levels double every 1-2 d, peak at 8-10 wk, then fall to a plateau until delivery
    - ♦ levels less than expected by dates suggest: ectopic pregnancy, abortion, or inaccurate dates
    - ♦ levels higher than expected suggest: multiple gestation, molar pregnancy, trisomy 21, or inaccurate dates
- **U/S**
  - transvaginal
    - ♦ 5 wk: gestational sac visible ( $\beta$ -hCG  $\geq 1,200$ -1,500 mIU/mL)
    - ♦ 6 wk: fetal pole seen
    - ♦ 7-8 wk: fetal heart tones visible
  - transabdominal
    - ♦ 6-8 wk: intrauterine pregnancy visible ( $\beta$ -hCG  $\geq 6,500$  mIU/mL)



### β-hCG Rule of 10s

10 IU at time of missed menses  
100,000 IU at 10 wk (peak)  
10,000 IU at term



### Trimesters

- T1 (first trimester): 0-12 wk
- T2 (second trimester): 12-28 wk
- T3 (third trimester): 28-40 wk
- Normal pregnancy term: 37-42 wk



## Maternal Physiology

**Table 1. Physiologic Changes During Pregnancy**

<b>Skin</b>	Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation) Other: spider angiomas, palmar erythema due to increased estrogen, striae gravidarum due to connective tissue changes
<b>Cardiovascular</b>	Hyperdynamic circulation Increased CO, HR and blood volume Decreased BP due to decreased PVR Enlarging uterus compresses IVC and pelvic veins Decreased venous return leads to risk of hypotension Increased venous pressure leads to risk of varicose veins, hemorrhoids, leg edema
<b>Hematologic</b>	Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit Increased leukocyte count but impaired function leads to improvement in autoimmune diseases Gestational thrombocytopenia: mild (platelets $> 70,000/\mu\text{L}$ ) and asymptomatic, normalizes within 2-12 wk following delivery Hypercoagulable state: increased risk of DVT and PE but also decreased bleeding at delivery
<b>Respiratory</b>	Increased incidence of nasal congestion and epistaxis Increased $\text{O}_2$ consumption to meet increased metabolic requirements Elevated diaphragm i.e. patient appears more "barrel-chested" Increased minute ventilation leads to decreased $\text{CO}_2$ resulting in mild respiratory alkalosis that helps $\text{CO}_2$ diffuse across the placenta from fetal to maternal circulation No change in VC and $\text{FEV}_1$ Decreased TLC, FRC, and RV
<b>Gastrointestinal</b>	GERD due to increased intra-abdominal pressure and progesterone (causing decreased sphincter tone and delayed gastric emptying) Increased gallstones due to progesterone causing increased gallbladder stasis Constipation and hemorrhoids due to progesterone causing decreased GI motility
<b>Genitourinary</b>	Increased urinary frequency due to increased total urinary output Increased incidence of UTI and pyelonephritis due to urinary stasis (see <i>Urinary Tract Infection</i> , OB20) Glycosuria that can be physiologic especially in the 3rd trimester; must test for GDM Ureters and renal pelvis dilation ( $R > L$ ) due to progesterone-induced smooth muscle relaxation and uterine enlargement Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 35-44 mmol/L), uric acid, and BUN
<b>Neurologic</b>	Increased incidence of carpal tunnel syndrome and Bell's palsy
<b>Endocrine</b>	Thyroid: moderate enlargement and increased basal metabolic rate Increased total thyroxine and thyroxine binding globulin (TBG) Free thyroxine index and TSH levels are normal Adrenal: maternal cortisol rises throughout pregnancy (total and free) Calcium: decreased total maternal $\text{Ca}^{2+}$ due to decreased albumin Free ionized $\text{Ca}^{2+}$ (i.e. active) proportion remains the same due to parathyroid hormone (PTH), results in increased bone resorption and gut absorption, increased bone turnover (but no loss of bone density due to estrogen inhibition)

## Prenatal Care

- provided by obstetrician, family doctor, midwife, or multidisciplinary team (based on patient preference and risk factors)
- Antenatal Records (province specific)



### Family doctors and midwives to consider OB consultation if:

- Insulin-dependent GDM
  - VBAC
  - HTN
  - Multiple gestation
  - Malpresentation
  - Active antepartum hemorrhage
  - PTL/PPROM
  - Failure to progress/descend
  - Induction/augmentation if high risk
  - Tears: 3rd or 4th degree
  - Retained placenta
- Note: Guidelines vary by institution.



Advise all women capable of becoming pregnant to supplement their diet with 0.4 mg/d of folic acid (CTFPHC Grade II-2-A Evidence).



Sometimes GP is used to describe gravida and parity. In this case, parity is used to describe number of term and premature infants delivered.



In history of previous pregnancies, **ALWAYS** ask:  
GTPAL  
Year  
Sex  
Weight  
Gestational age (GA)  
Mode of delivery  
Length of labour  
Complications



Ask every woman about abuse – not just those whose situations raise suspicion of abuse AND ask as early as possible in pregnancy.

ALPHA form <http://www.ecmaj.ca/content/159/6/677.full.pdf>



Tests for HIV, prenatal and genetic screening are voluntary and require proper counselling and informed consent before proceeding.

## Preconception Counselling

- 3-8 wk GA is a critical period of organogenesis, so early preparation is vital
- past medical history:** optimize medical illnesses and necessary medications prior to pregnancy (see *Medical Conditions in Pregnancy*, OB13, and *Medications in Pregnancy*, OB10)
- supplementation**
  - folic acid: encourage diet rich in folic acid and supplement 8-12 wk preconception until end of T1 to prevent NTDs
    - 0.4-1 mg daily in all women, 5 mg if previous NTD, anti-epileptic medications, diabetes mellitus or BMI >35 kg/m<sup>2</sup>
  - iron supplementation, prenatal vitamins
- risk modification**
  - lifestyle: balanced nutrition and physical fitness
  - medications: patients with chronic diseases should discuss whether their medications may be teratogenic prior to conception so they may be adjusted. It is not advised to stop medications abruptly when becoming pregnant
  - infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV
  - genetic testing as appropriate for high risk groups (see *Prenatal Screening* section, Table 2, OB5); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay or birth anomalies
  - social: alcohol, smoking, drug use, domestic violence
    - use ALPHA form to screen for antenatal risk factors associated with poor postpartum family outcomes (woman abuse, child abuse, postpartum depression, marital dysfunction and increased physical illness)

## Initial Prenatal Visit

- usually within 12 wk of the first day of LMP or earlier if <20 or >35 yr old or other risk factors are present
- Antenatal Records are filled out on the first prenatal visit

### History

- gestational age by dates from the first day of the LMP
- if LMP unreliable, get a dating ultrasound (see below)
- EDC using Naegle's Rule:
  - 1st day of LMP + 7 d – 3 mo
  - e.g. LMP = 1 Apr 2013, EDC = 8 Jan 2014 (modify if cycle >28 d by adding number of d >28)
- history of present pregnancy (e.g. bleeding, nausea, vomiting)
- history of all previous pregnancies
- past medical history, past gynecological history
- prescription and non-prescription medications
- family history: genetic disease, birth defects, multiple gestation
- social history: smoking, alcohol, drug use, domestic violence (use ALPHA form), consanguinity

### Physical Examination

- complete exam to obtain baseline patient information
- BP and weight important for interpreting subsequent changes
- pelvic exam

### Investigations

- bloodwork
  - CBC, blood group and type, Rh antibodies, infection screening as per preconception counselling
- urine R&M, C&S
  - screen for bacteriuria and proteinuria
- pelvic exam
  - Pap smear (unless done within last 6-12 mo), cervical culture for *N. gonorrhoeae* (GC) and *C. trachomatis*, vaginal swab for bacterial vaginosis (BV)

## Subsequent Prenatal Visits

### Timing

- for uncomplicated pregnancies, q4-6wk until 28 wk, q2wk from 28 to 36 wk and weekly from 36 wk until delivery

### Assess at Every Visit

- record estimated GA
- history of present pregnancy: fetal movements, uterine bleeding, leaking, cramping
- physical exam: BP, weight gain, SFH, Leopold's maneuvers (T3) for lie, position and presentation of fetus
- investigations: urinalysis for glucosuria, ketones, proteinuria; fetal heart rate starting at 12 wk using Doppler U/S

### Leopold's Maneuvers

- performed after 30-32 wk gestation
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver: to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

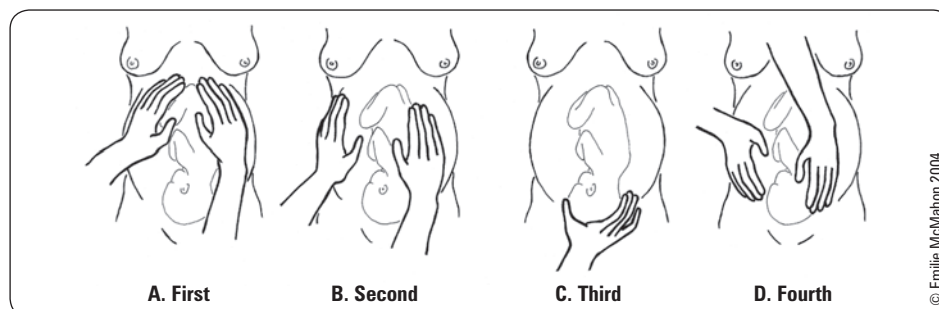


Figure 2. Leopold's maneuvers (T3)

Reprinted with permission from Essentials of Clinical Examination Handbook, 6th ed. Lincoln, McSheffrey, Tran, Wong



### Symphysis Fundal Height (SFH)

- 12 wk: Uterine fundus at pubic symphysis
- 20 wk: Fundus at umbilicus, SFH should be within 2 cm of GA between 20-36 wk
- 37 wk: Fundus at sternum



### Small for Dates

- Date miscalculation
- IUGR
- Fetal demise
- Oligohydramnios

### Large for Dates

- Date miscalculation
- Multiple gestation
- Polyhydramnios
- LGA (familial, diabetes)

## Prenatal Screening and Diagnostic Tests

### SCREENING TESTS

- testing should only occur following counselling and with the informed consent from the patient

Table 2. High-Risk Population Screening Tests

Disease [Inheritance]	Population(s) at Risk	Screening Test(s)
<b>Thalassemia [AR]</b>	<b>Mediterranean, South East Asian, Western Pacific, African, Middle Eastern, Caribbean, South American</b>	CBC (MCV and MCH), Hb electrophoresis or HPLC
<b>Sickle Cell [AR]</b>	<b>African, Caribbean, Mediterranean, Middle Eastern, Indian, South American</b>	CBC (MCV and MCH), Hb electrophoresis or HPLC
<b>Cystic Fibrosis (CF) [AR]</b>	Mediterranean, Finnish, Caucasian, or FHx	CFTR gene DNA analysis
<b>Tay Sachs Disease [AR]</b>	Ashkenazi Jewish*, French Canadians, Cajun	Enzyme assay HEXA, or DNA analysis HEXA gene
<b>Fragile X Syndrome [X-linked]</b>	Family history – confirmed or suspected	DNA analysis: FMR-1 gene

AR = autosomal recessive; HPLC = high performance liquid chromatography; HEXA = hexosaminidase A

\*If both partners are Ashkenazi Jewish, test for Canavan disease and Familial Dysautonomia (FD); if family history of a specific condition, look for carrier status: e.g. Gaucher, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners positive, refer for genetic counselling

**Table 3. Gestation-Dependent Screening Investigations**

Gestational Age (wk)	Investigations	Details
8-12	Dating U/S, initial Pap smear, chlamydia/gonorrhea cultures	
10-12	CVS	
11-14	FTS IPS Part 1	Measures 1. Nuchal translucency on U/S 2. $\beta$ -hCG 3. PAPP-A
11-14	Nuchal translucency U/S	
15-16 to term	Amniocentesis	
15-20	IPS Part 2	Measures 1. MSAFP 2. $\beta$ -hCG 3. Unconjugated estrogen (estriol or $\mu$ E3) 4. Inhibin A
15-20	Maternal serum screen (MSS) (or MSAFP only for patients who did FTS earlier)	Measures 1. MSAFP 2. $\beta$ -hCG 3. Unconjugated estrogen (estriol or $\mu$ E3)
18-20 to term	Fetal movements (quickening)	
18-20	U/S for dates, fetal growth and anatomy assessment	
24-28	50 g OGCT	
28	Repeat CBC RhIG for all Rh negative women	
35-37	GBS screen	
6 wk postpartum	Discuss contraception, menses, breastfeeding, depression, mental health, support Physical exam: breast exam, pelvic exam including Pap smear (only if due as per provincial screening)	

Maternal serum screen is also referred to as Triple Screen. If Inhibin A is also tested, it is referred to as Quadruple Screen

Ideally testing for MSS and IPS Part 2 occur between 15-18 wk to give women more time to make decisions and move ahead with diagnostic testing should the result screen be positive



**Routine T2 U/S at 18-22 wk, helps determine:**

- Number of fetuses
- GA (if no prior U/S)
- Location of placenta
- Fetal anomalies

## ULTRASOUND SCREENING

- dating ultrasound best done between 8-12 wk GA (most accurate form of pregnancy dating)
  - measurement of crown-rump length (margin of error  $\pm$  5 d)
  - change EDC to U/S date if  $>1$  wk discrepancy from EDC based on LMP
- NTUS at 11-14 wk GA
  - measures the amount of fluid behind the neck of the fetus
  - early screen for Trisomy 21 (may also detect cardiac and other aneuploidies like Turner's syndrome)
  - NT measurement is necessary for the FTS and IPS Part 1
- fetal growth and anatomy ultrasound routinely done at 18-20 wk GA (margin of error  $\pm$  7 d) (see [Pediatrics](#), P41 for congenital anomalies)
- earlier or subsequent ultrasounds performed when medically indicated

**Table 4. Comparison of FTS, MSS and IPS**

First Trimester Screen (FTS)	Maternal Serum Screen (MSS)	Integrated Prenatal Screen (IPS)
11-14 wk	15-20 wk	Nuchal translucency on 12 wk U/S FTS at 11-14 wk MSS + inhibin A at 15-20 wk
Risk estimate for 1. Down syndrome (Trisomy 21): increased NT, increased $\beta$ -hCG, decreased PAPP-A  Note: does not measure risk of open neural tube defect (oNTD) and should be combined with MSAFP at 16 wk Useful where patient wants results within the first trimester More accurate estimate of Down syndrome risk than MSS, sensitivity $\sim$ 85% (when combined with age) 5% false positive rate Patients with positive screen should be offered CVS or amniocentesis	Risk estimate for 1. oNTD: increased MSAFP (sensitivity 80-90%) 2. Trisomy 21: decreased MSAFP, increased $\beta$ -hCG, decreased $\mu$ E3 (sensitivity 65%) 3. Trisomy 18: decreased MSAFP, decreased $\beta$ -hCG, decreased $\mu$ E3 (sensitivity 80%) Only offered alone if patient missed the time window for IPS or FTS 8% baseline false positive rate for Trisomy 21, lower for oNTD and Trisomy 18 Patients with positive screen should be offered U/S or amniocentesis	Risk estimate for oNTD, Trisomy 21, Trisomy 18 Sensitivity $\sim$ 85-90% 2% false positive rate Patients with positive screen should be offered U/S and/or amniocentesis

Note: In twins, FTS, MSS and IPS are not applicable; screen with NT for chromosomal abnormalities and MSAFP for oNTDs



## DIAGNOSTIC TESTS

### Indications

- maternal age  $>35$  (increased risk of chromosomal anomalies)
- risk factors in current pregnancy:
  - abnormal U/S
  - abnormal prenatal screen (IPS, FTS, or MSS)
- past history/family history of:
  - previous pregnancy with chromosomal anomaly or genetic disease
  - either parent a known carrier of a genetic disorder or balanced translocation
  - family history of chromosomal anomaly, genetic disorder, birth defect, or undiagnosed mental retardation
  - consanguinity
  - three or more spontaneous abortions

### AMNIOCENTESIS

- U/S-guided transabdominal extraction of amniotic fluid

### Indications

- identification of genetic anomalies (15-16 wk gestation) as per indications above
- assessment of fetal lung maturity (T3) via the L/S ratio (lecithin:sphingomyelin)
  - if  $>2:1$ , RDS is less likely to occur

### Advantages

- also screens for oNTD (acetylcholinesterase and amniotic AFP) – 96% accurate
- in women  $>35$  yr, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- more accurate genetic testing than CVS

### Disadvantages

- 1/400 – 1/500 risk of spontaneous abortion
- results take 14-28 d; FISH can be done on chromosomes X, Y, 21, 13, 18 to give preliminary results in 48 h

### CHORIONIC VILLUS SAMPLING

- biopsy of fetal-derived chorion using a trans-abdominal needle or trans-cervical catheter at 10-12 wk

### Advantages

- enables pregnancy to be terminated earlier than with amniocentesis
- rapid karyotyping and biochemical assay within 48 h, including FISH analysis
- high sensitivity and specificity

### Disadvantages

- 1-2% risk of spontaneous abortion
- does not screen for oNTD
- 1-2% incidence of genetic mosaicism “false negative” results

### ISOIMMUNIZATION SCREENING

#### Definition

- isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigenic stimulation with RBC of another individual

#### Etiology

- maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
- in pregnancy, anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
- overall risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16%
- sensitization routes
  - incompatible blood transfusions
  - previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy)
  - invasive procedures in pregnancy (e.g. prenatal diagnosis, cerclage, D&C)
  - any type of abortion
  - labour and delivery



#### DDx of Increased MSAFP

- Incorrect GA
- $>1$  fetus (e.g. twins)
- Fetal demise
- oNTD
- Abdominal wall defects (e.g. omphalocele)



#### DDx of Decreased MSAFP

- Incorrect GA
- Gestational trophoblastic neoplasia
- Missed abortion
- Chromosomal anomalies
- Maternal diabetes



Compared to CVS, amniocentesis has a higher accuracy of prenatal cytogenetic diagnosis (99.8% vs. 97.5%) and lower risk of spontaneous abortion (0.5% vs. 1-2%).



#### Risk Factors for Neural Tube Defects

##### GRIMM

**Genetics:** family history of NTD (risk of having second child with NTD is increased to 2-5%), consanguinity, chromosomal (characteristic of trisomy 13, 18, and 21)

**Race:** European Caucasians  $>$  African Americans, 3-fold higher in Hispanics

**Insufficient vitamins:** zinc and folate

**Maternal chronic disease** (e.g. diabetes)

**Maternal use of anti-epileptic drugs**

General population risk for NTD is 0.1%.

## Investigations

- routine screening with indirect Coombs test at first visit for blood group, Rh status, and antibodies
- Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage by estimating volume of fetal blood volume that entered maternal circulation.
- detailed U/S for hydrops fetalis

## Prophylaxis

- exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
- Rhogam® (300 µg) given to all Rh negative and antibody screen negative women in the following scenarios:
  - routinely at 28 wk GA (provides protection for ~12 wk)
  - within 72 h of the birth of an Rh positive fetus
  - with a positive Kleihauer-Betke test
  - with any invasive procedure in pregnancy (CVS, amniocentesis)
  - in ectopic pregnancy
  - with miscarriage or therapeutic abortion (only 50 µg required)
  - with an antepartum hemorrhage
- if Rh negative and Ab screen positive, follow mother with serial monthly Ab titres throughout pregnancy ± serial amniocentesis as needed (Rhogam® has no benefit)

## Investigations

- MCA dopplers are done to assess degree of fetal anemia or if not available bilirubin is measured by serial amniocentesis to assess the severity of hemolysis
- cordocentesis for fetal Hb should be used cautiously (not first line)

## Treatment

- falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
- intrauterine transfusion of O-negative pRBCs may be required for severely affected fetus or early delivery of the fetus for exchange transfusion

## Complications

- anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, ascites
- severe cases can lead to fetal hydrops (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)

## GROUP B *STREPTOCOCCUS* SCREEN

### Epidemiology

- 15-40% vaginal carrier rate

### Risk Factors (for neonatal disease)

- GBS bacteriuria during current pregnancy even if treated
- previous infant with invasive GBS infection
- preterm labour <37 wk
- ruptured membranes >18 h before delivery
- intrapartum maternal temperature ≥38°C
- positive GBS screen during current pregnancy

### Clinical Features

- not harmful to mother
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia, and death)

### Investigations

- offer screening to all women at 35-37 wk with vaginal and anorectal swabs for C&S

### Treatment

- treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
- indications for antibiotic prophylaxis: positive GBS screen or GBS status unknown and one of the risk factors (see above)
- antibiotics for GBS prophylaxis
  - penicillin G 5 million units IV then 2.5 million units IV q4h until delivery
  - penicillin allergic but not at risk for anaphylaxis: cefazolin 2 g IV then 1 g q8h
  - penicillin allergic and at risk for anaphylaxis: clindamycin 900 mg IV q8h or erythromycin 500 mg IV q6h
- if fever, broad spectrum antibiotic coverage is advised



#### Rh Antibody Titre

A positive titre (≥1:16) indicates an increased risk of fetal hemolytic anemia.



Standard dose of 300 µg of Rhogam sufficient for 30 mL of fetal blood. Give additional 10 µg of Rhogam for every mL of fetal blood over 30 mL.



#### Indications for Intrapartum Antibiotic GBS Prophylaxis

Centers for Disease Control and Prevention. Prevention of Perinatal Group B Streptococcal Disease. *MMWR* 2010;59(RR-10):14

- Previous infant with invasive GBS disease
- GBS bacteriuria during any trimester of the current pregnancy
- Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy
- Unknown GBS status at the onset of labour (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 wk gestation
  - Amniotic membrane rupture ≥18 h
  - Intrapartum temperature ≥100.4°F (≥38.0°C)
- Intrapartum nucleic-acid amplification test positive for GBS

# Counselling of the Pregnant Woman

## Nutrition

- Canada's Food Guide to Healthy Eating suggests:
  - 3-4 servings of milk products daily (greater if multiple gestation)
  - a daily caloric increase of ~100 cal/d in the 1st trimester, ~300 cal/d in the second and third trimesters and ~450 cal/d during lactation
  - daily multivitamin should be continued in the 2nd trimester for women who do not consume an adequate diet; otherwise routine vitamin supplementation is not necessary (avoid excess vitamin A)
- nutrients important during pregnancy
  - folate: 0.4 mg/d for first 12 wk (5 mg/d if high risk)
    - ♦ supports maternal increase in blood volume, growth of maternal and fetal tissue, decreases incidence of neural tube defects
    - ♦ foods rich in folic acid include: spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn and oranges
  - calcium: 1200-1500 mg/d
    - ♦ maintains integrity of maternal bones, skeletal development of fetus, breast milk production
  - vitamin D: 1000 IU
    - ♦ promotes calcium absorption
  - iron: 0.8 mg/d in T1, 4-5 mg/d in T2 and >6 mg/d in T3
    - ♦ supports maternal increase in blood cell mass, supports fetal and placental tissue
    - ♦ required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
    - ♦ iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see *Iron Deficiency Anemia*, OB13)
  - essential fatty acids – supports fetal neural and visual development
    - ♦ contained in vegetable oils, margarines, peanuts, fatty fish

### Caffeine

- diuretic and stimulant that readily crosses placenta
- less than 200 mg per day is not thought to contribute to miscarriage or preterm birth (ACOG)
  - relationship between caffeine and IUGR is unknown (ACOG)
  - SOCG states 1-2 cups/d are safe during pregnancy

### Herbal Teas and Preparations

- not enough scientific information about safety of various herbs and herbal products to recommend their use during pregnancy
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- chamomiles have been reported to exhibit adverse effects on the uterus

### Food Borne Illnesses

- microbiological contamination of food may occur through cross-contamination and/or improper food handling
  - listeriosis (*Listeria monocytogenes*) and toxoplasmosis (*Toxoplasma gondii*) are of concern during pregnancy
  - avoid consumption of raw meats, fish, poultry, raw eggs, and unpasteurized dairy products
  - avoid soft cheeses, deli meats, smoked salmon and pates as they may be sources of *Listeria*
- chemical contamination of food
  - current guideline for mercury of 0.5 ppm in fish is not considered harmful for the general population, including pregnant women
  - Health Canada advises pregnant women to limit consumption of top predator fish such as shark, swordfish, king mackerel, tilefish, and fresh/frozen tuna (not canned tuna) to one meal per month



#### Sources of Caffeine

- 5 oz cup coffee: 40-180 mg
- 5 oz brewed tea: 20-90 mg
- 12 oz cola: 46 mg
- Red Bull®: 67 mg
- Dark chocolate bar: 10 mg
- 8 oz hot chocolate: 5 mg



#### Herbal Teas Considered Safe in Moderation (2-3 cups/d)

- Citrus peel
- Ginger
- Lemon balm
- Linden flower – not with prior cardiac condition
- Orange peel
- Rose hip

## Lifestyle

- exercise under physician guidance
- absolute contraindications
  - ruptured membranes, preterm labour, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestations (>3), placenta previa after 28th wk, persistent 2nd or 3rd trimester bleeding, uncontrolled type I diabetes, uncontrolled thyroid disease, or other serious cardiovascular, respiratory or systemic disorder

- relative contraindications
  - previous preterm birth, mild/moderate cardiovascular or respiratory disorder, anemia (Hb  $\leq 100$  g/L), malnutrition or eating disorder, twin pregnancy after 28th wk, other significant medical conditions
- weight gain: optimal gain depends on pre-pregnancy weight (varies from 6.8-18.2 kg)
- work: strenuous work, extended hours and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
- travel: not harmful, but stress related to travel may be associated with preterm labour
  - air travel is acceptable in second trimester; airline cutoff for travel is 36-38 wk gestation depending on the airline to avoid giving birth on the plane
- sexual intercourse: may continue, except in patients at risk for: abortion, preterm labour, or placenta previa; breast stimulation may induce uterine activity and is discouraged in high-risk patients near term
- smoking: assist/encourage to reduce or quit smoking
  - increased risk of: decreased birth weight, placenta previa/abruption, spontaneous abortion, preterm labour, stillbirth
- alcohol: no amount of alcohol is safe in pregnancy. Encourage abstinence from alcohol during pregnancy; alcohol increases incidence of abortion, stillbirth, and congenital anomalies
  - fetal alcohol syndrome (see [Pediatrics](#), P24)
- cocaine: microcephaly, growth retardation, prematurity, abruptio placentae



#### Expected Weight Gain

BMI (kg/m <sup>2</sup> )	Weight (kg)
<19	12.7-18.2
19-25	11.3-15.9
>25	6.8-11.3

**General Rule:** 1-3.5 kg/wk during T1, then 0.45 kg/wk until delivery



## Medications

- most drugs cross the placenta to some extent
- very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
- use any drug with caution and only if necessary
- analgesics: acetaminophen preferable to ASA or ibuprofen

**Table 5. Documented Adverse Effects, Contraindicated**

Contraindicated Medication	Adverse Effect
ACE inhibitors	Fetal renal defects, IUGR, oligohydramnios
tetracycline	Stains infant's teeth, may affect long bone development
retinoids (e.g. Accutane®)	CNS, craniofacial, cardiac, and thymic anomalies
DES (and other estrogenic or androgenic compounds)	Vaginal adenosis, adenocarcinoma, uterine malformation in females exposed to DES in utero
misoprostol	Mobius syndrome (congenital facial paralysis with or without limb defects, spontaneous abortion, preterm labour)

**Table 6. Documented Adverse Effects, Weigh Benefits vs. Risks and Consider Medication Change**

Medication	Adverse Effect
phenytoin	Fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmorphogenesis, congenital anomalies)
valproate	oNTD in 1%
carbamazepine	oNTD in 1-2%
lithium	Ebstein's cardiac anomaly, goitre, hyponatremia
warfarin	Increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR, fetal warfarin syndrome (nasal hypoplasia, epiphyseal stippling, optic atrophy, mental retardation, intracranial hemorrhage)
erythromycin	Maternal liver damage (acute fatty liver)
sulpha drugs	Anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3
chloramphenicol	Grey baby syndrome (fetal circulatory collapse 2° to toxic accumulation)



#### Drug Resources during Pregnancy and Breastfeeding

- Motherisk at the Hospital for Sick Children in Toronto: [www.motherisk.org](http://www.motherisk.org)
- Hale T. Medications and mothers' milk, 11th ed. Pharmasoft Publishing, 2004



Trimethoprim is a folic acid antagonist associated with NTD.

## Immunizations

### Intrapartum

- administration is dependent on the risk of infection vs. risk of immunization complications
- safe: tetanus toxoid, diphtheria, influenza, hepatitis B
- avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, varicella
- contraindicated: rubella, oral typhoid

### Postpartum

- rubella vaccine for all non-immune mothers
- hepatitis B vaccine should be given to infant within 12 h of birth if maternal status unknown or positive – follow-up doses at 1 and 6 mo
- human papillomavirus (HPV) vaccine – if meets criteria

## Radiation

- ionizing radiation exposure is considered teratogenic at high doses
  - if indicated for maternal health, should be done
- imaging not involving direct abdominal/pelvic high dosage is not associated with adverse effects
  - higher dosage to fetus: plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen, pelvis, lumbar spine
- most investigations involve minimal radiation exposure (see Table 7)
- radioactive isotopes of iodine are contraindicated
- no known adverse effects from U/S or MRI



### Radiation in Pregnancy

- Necessary amount to cause miscarriage: >5 rads
- Necessary amount to cause malformations: >20-30 rads

**Table 7. Approximate Fetal Doses from Common Diagnostic Procedures**

Examination	Estimated Fetal Dose (rad)	Number of Exams Safe in Pregnancy
<b>Plain Film</b>		
Abdomen	0-14	35
Pelvis	0-11	45
Lumbar spine	0-17	29
Thoracic spine	0.009	555
Chest (2 views)	<0.001	5000
<b>CT</b>		
Abdomen	0-8	6
Pelvis	2-5	2
Lumbar spine	0-24	20
Chest	0.006	833

Adapted from Cohen-Kerem, et al. 2005 and Valentin, 2000

## Termination of Pregnancy

- see [Gynecology](#), GY9

### Definition

- active termination of a pregnancy before fetal viability (usually <500 g or 20 wk GA)

### Indications

- inability to carry a pregnancy to term due to medical or social reasons (including patient preference)

### Management

- medical
  - <9 wk: methotrexate + misoprostol
  - >12 wk: prostaglandins (intra- or extra-amniotically or IM) or misoprostol
- surgical
  - <12 wk: dilatation + vacuum aspiration ± curettage
  - >12 wk: dilatation and evacuation, early induction of labour
  - common complications: pain or discomfort
  - less common complications: hemorrhage, perforation of uterus, laceration of cervix, risk of infertility, infection/endometritis, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), retained products of conception
- counselling
  - supportive and counselling services
  - future contraception and family planning services
  - ensure follow-up



### CMA policy (1988)

"Induced abortion should be uniformly available to all women in Canada" and "there should be no delay in the provision of abortion services".



Terminations are generally done until the stage of viability (~23.5 wk), although this varies depending on the provider.



### Induced Abortion Statistics

- Rate per 1,000 women (all ages): 13.7
- 31.4% of all abortion services are accessed by women aged 20-24

Adapted from Statistics Canada. Induced abortion statistics. 82-223-XWE, 2005;16

# Prenatal Fetal Monitoring

## Fetal Movements

- patients will generally first notice fetal movement ("quickening") at 18-20 wk in primigravidas; can occur 1-2 wk earlier in multigravidas; can occur 1-2 wk later if placenta is implanted on the anterior wall of uterus
- if the patient is concerned about decreased fetal movement, she is counselled to choose a time when the fetus is normally active to count movements (usually recommended after 28 wk)
  - if there is a subjective decrease in fetal movement, try drinking juice, eating, changing position or moving to a quiet room and count for 2 h. There should be  $\geq 6$  movements in 2 h
  - if there are  $< 6$  movement counts in 2 h, patient should present to labour and delivery triage



### DDx of Decreased Fetal Movements

#### DASH

Death of fetus  
Amniotic fluid decreased  
Sleep cycle of fetus  
Hunger/Thirst



## NON-STRESS TEST (NST)

### Definition

- FHR tracing  $\geq 20$  min using an external Doppler to assess FHR and its relationship to fetal movement (see *Fetal Monitoring in Labour*, OB34)

### Indication

- any suggestion of uteroplacental insufficiency or suspected compromise in fetal well-being

Table 8. Classification of Antepartum Non-Stress Test

Parameter	Normal NST (Previously "Reactive")	Atypical NST (Previously "Non-Reactive")	Abnormal NST (Previously "Non-Reactive")
Baseline	110-160 bpm	100-110 bpm or $> 160$ bpm for $< 30$ min Rising baseline	Bradycardia $< 100$ bpm Tachycardia $> 160$ for $> 30$ min Erratic baseline
Variability	6-25 bpm (moderate) $\leq 5$ (absent or minimal) for $< 40$ min	5 (absent or minimal) for 40-80 min	$\leq 5$ for 80 min Sinusoidal 25 bpm for $> 10$ min
Decelerations	None or occasional variable $< 30$ s	Variable decelerations 30-60 s duration	Variable decelerations $> 60$ s Late deceleration(s)
Accelerations in Term Fetus	2 accelerations with acme of $\geq 15$ bpm, lasting 15 s or over $< 40$ min of testing	2 accelerations with acme of $\geq 15$ bpm, lasting 15 s in 40-80 min	$< 2$ accelerations with acme of $\geq 15$ bpm, lasting 15 s in $> 80$ min
Accelerations in Preterm Fetus ( $< 32$ wk)	$> 2$ accelerations with acme of $> 10$ bpm, lasting 10 s in $< 40$ min	$< 2$ accelerations with acme of $> 10$ bpm, lasting 10 s in 40-80 min	$< 2$ accelerations with acme of $> 10$ bpm, lasting 10 s in $> 80$ min
Action	FURTHER ASSESSMENT OPTIONAL, based on total clinical picture	FURTHER ASSESSMENT REQUIRED	URGENT ACTION REQUIRED An overall assessment of the situation and further investigation with U/S or BPP is required. Some situations will require delivery



Normal NST: 2 accels,  $> 15$  bpm from baseline, lasting  $> 15$  s in 20 min.

Adapted from SOGC, Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline, September 2007

### Operating Characteristics

- false positive rate depends on duration; false negative rate = 0.2-0.3%

### Interpretation

- normal: at least 2 accelerations of FHR  $> 15$  bpm from the baseline lasting  $> 15$  s, in 20 min
- abnormal:  $< 2$  accelerations of FHR in 40 min
- if no observed accelerations or fetal movement in the first 20 min, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 min
- if NST abnormal, then perform BPP

## BIOPHYSICAL PROFILE

### Definition

- U/S assessment of the fetus  $\pm$  NST

### Indications

- abnormal or atypical NST
- post-term pregnancy
- decreased fetal movement
- any other suggestion of fetal distress or uteroplacental insufficiency



### Operating Characteristics

- false positive rate  $\leq 30\%$ , false negative rate = 0.1%

**Table 9. Scoring of the BPP**

Parameter	Reassuring (2 points)	Non-Reassuring (0 points)
<b>AFV*</b>	Fluid pocket of 2 cm in 2 axes	Oligohydramnios
<b>Breathing</b>	At least one episode of breathing lasting at least 30 s	No breathing
<b>Limb Movement</b>	Three discrete movements	Two or less
<b>Fetal Tone</b>	At least one episode of limb extension followed by flexion	No movement

\*AFV is a marker of chronic hypoxia, all other parameters indicate acute hypoxia



#### Reassuring BPP (8/8)

##### LAMB

Limb extension + flexion

AFV 2 cm x 2 cm

Movement (3 discrete)

Breathing (one episode x 30 s)

### Interpretation

- 8: perinatal mortality rate 1:1000; repeat BPP as clinically indicated
- 6: perinatal mortality rate 31:1000; repeat BPP in 24 h
- 0-4: perinatal mortality rate 200:1000; deliver fetus if benefits of delivery outweigh risks

## Medical Conditions in Pregnancy

### Iron and Folate Deficiency Anemia

**Table 10. Iron Deficiency and Folate Deficiency Anemia**

	Iron Deficiency Anemia	Folate Deficiency Anemia
<b>Etiology</b>	See <a href="#">Hematology</a> , H14	See <a href="#">Hematology</a> , H23
<b>Epidemiology</b>	Responsible for 80% of causes of non-physiologic anemia during pregnancy	Incidence varies from 0.5-25% depending on region, population, diet
<b>Clinical Features</b>	See <a href="#">Hematology</a> , H14	See <a href="#">Hematology</a> , H23
<b>Investigations</b>	See <a href="#">Hematology</a> , H14	See <a href="#">Hematology</a> , H24
<b>Management</b>	Prevention (non-anemic): 30 mg elemental iron/d (met by most prenatal vitamins) Treatment (anemic): 30-120 mg elemental iron/d 325 mg ferrous fumarate = 106 mg elemental $\text{Fe}^{2+}$ ; 325 mg ferrous sulfate = 65 mg elemental $\text{Fe}^{2+}$ ; 325 mg ferrous gluconate = 36 mg elemental $\text{Fe}^{2+}$	Prevention: 0.4-1 mg folic acid PO daily for 1-3 mo preconceptually and throughout T1, or 5 mg folic acid per day with past history of oNTD, diabetes or anti-epileptic medication use
<b>Complications</b>	Maternal: angina, CHF, infection, slower recuperation, preterm labour Fetal: decreased oxygen carrying capacity leading to fetal distress, IUGR and low birth weight	Maternal: decreased blood volume, nausea, vomiting, anorexia Fetal: neural tube defects in T1, low birth weight, prematurity
<b>Notes</b>	Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg) and losses (200 mg) – more needed for multiple gestations	Minimum daily requirement is 0.4 mg Most often associated with iron deficiency anemia Folic acid is necessary for closure of neural tube during early fetal development (by day 28 of gestation)



### Diabetes Mellitus (DM)

#### Classification of Diabetes Mellitus

- Type 1 and Type 2 DM (see [Endocrinology](#), E6)
- GDM: onset of diabetes mellitus during pregnancy

#### Etiology

- Type 1 and Type 2 DM
- GDM: usually around 24-28 wk GA, anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → higher fasting glucose → leading to GDM and/or exacerbating pre-existing DM

#### Epidemiology

- 2-4% of pregnancies are complicated by DM



## MANAGEMENT

### A. TYPE 1 AND TYPE 2 DM

#### Preconception

- pre-plan and refer to high-risk clinic
- optimize glycemic control
- counsel patient re: potential risks and complications
- evaluate for diabetic retinopathy, neuropathy, coronary artery disease

#### Pregnancy

- if already on oral medication, generally switch to insulin therapy
  - continuing glyburide or metformin controversial
  - teratogenicity unknown for other oral anti-hyperglycemics
- tight glycemic control
  - insulin dosage may need to be adjusted in T2 due to increased demand and increased insulin resistance
- monitor as for normal pregnancy plus initial 24 h urine protein and creatinine clearance, retinal exam, HbA1c
  - HbA1c: >140% of pre-pregnancy value associated with increased risk of spontaneous abortion and congenital malformations
- increased fetal surveillance (BPP, NST)

#### Labour

- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose and blood pressure control)
- can wait for spontaneous labour if blood glucose well-controlled and BPP normal
- induce by 40 wk
- type of delivery
  - increased risk of cephalopelvic disproportion (CPD) and shoulder dystocia with babies >4,000 g (8.8 lbs)
  - elective C/S for predicted birthweight >4,500 g (9.9 lbs) (controversial)
- monitoring
  - during labour monitor blood glucose q1h with patient on insulin and dextrose drip
  - aim for blood glucose between 3.5 to 6.5 mmol/L to reduce the risk of neonatal hypoglycemia

#### Postpartum

- insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
- no insulin is required for 48-72 h postpartum in most Type 1 DM
- monitor glucose q6h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >8 mmol/L

### B. GESTATIONAL DIABETES MELLITUS

#### Screening + Diagnosis

- at 24-28 wk GA
- pregnant females age >25 or age <25 yr with >1 risk factor (see sidebar)
- 1 h, 50 g Oral Glucose Challenge Test (OGCT): not fasting
  - PG <7.8 mmol/L = no GDM
  - PG ≥7.8-10.3 mmol/L = further investigation with OGTT
  - PG ≥10.3 mmol/L = GDM
- 2 h, 75 g Oral Glucose Tolerance Test (OGTT): fasting
  - FPG ≥5.3 mmol/L
  - PG 1 h ≥10.6 mmol/L
  - PG 2 h ≥8.9 mmol/L
    - ♦ 2/3 of the above = GDM
    - ♦ 1/3 of the above = impaired glucose tolerance (IGT)

#### Management

- treat both GDM and IGT
- first line is management through diet modification and increased physical activity
- tight glycemic control optimal as in Type 1 and Type 2 DM
- monitoring and timing of delivery as for Type 1 and Type 2 DM
- stop insulin and diabetic diet postpartum
- follow-up with 2 h, 75 g OGTT 6 wk-6 mo postpartum



Post-prandial blood glucose values seem to be the most effective at determining the likelihood of macrosomia or other adverse pregnancy outcomes.



#### Monitoring Glucose Levels

- Frequent measurements of blood glucose during pregnancy are advised for women with Type 1 or 2 diabetes to help prevent or treat both hypoglycemia and hyperglycemia, and also improves neonatal outcome
- Aim for FPG ≤5.3 mmol/L (95 mg/dL), 1 h post prandial
- PG ≤7.8 mmol/L (140 mg/dL), 2 h post prandial PG ≤6.7 mmol/L (120 mg/dL)
- Most women can be followed with monthly HbA1c determinations



#### Risk Factors for GDM:

- Age >25
- Obesity
- Ethnicity (Aboriginal, Hispanic, Asian, African)
- FHx of DM
- Previous history of GDM
- Previous child with birthweight >4.0 kg
- Polycystic ovarian syndrome
- Current use of glucocorticoids
- Essential hypertension or pregnancy-related hypertension

## Prognosis

- most maternal and fetal complications are related to hyperglycemia and its effects

## Long Term Maternal Complications

- Type 1 and Type 2 DM: risk of progressive retinopathy and nephropathy
- GDM: 50% risk of developing Type 2 DM in next 20 yr

**Table 11. Complications of DM in Pregnancy**

Maternal	Fetal
<b>Obstetric</b> <ul style="list-style-type: none"> <li>Hypertension/preeclampsia (especially if pre-existing nephropathy/proteinuria): insulin resistance is implicated in etiology of hypertension</li> <li>Polyhydramnios: maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal polyuria (a major source of amniotic fluid)</li> </ul>	<b>Growth Abnormalities</b> <ul style="list-style-type: none"> <li>Macrosomia: maternal hyperglycemia leads to fetal hyperinsulinism resulting in accelerated anabolism</li> <li>Intrauterine growth restriction (IUGR): due to placental vascular insufficiency</li> </ul>
<b>Diabetic Emergencies</b> <ul style="list-style-type: none"> <li>Hypoglycemia</li> <li>Ketoacidosis</li> <li>Diabetic coma</li> </ul>	<b>Delayed Organ Maturity</b> <ul style="list-style-type: none"> <li>Fetal lung immaturity: hyperglycemia interferes with surfactant synthesis (respiratory distress syndrome)</li> </ul>
<b>End-organ Involvement or Deterioration (occur in DM1 and DM2, not in GDM)</b> <ul style="list-style-type: none"> <li>Retinopathy</li> <li>Nephropathy</li> </ul>	<b>Congenital Anomalies (occur in DM1 and DM2, not in GDM)</b> <ul style="list-style-type: none"> <li>2-7x increased risk of cardiac (VSD), NTD, GU (cystic kidneys), GI (anal atresia), and MSK (sacral agenesis) anomalies due to hyperglycemia</li> <li>Note: Pregnancies complicated by GDM do not manifest an increased risk of congenital anomalies because GDM develops after the critical period of organogenesis (in T1)</li> </ul>
<b>Other</b> <ul style="list-style-type: none"> <li>Pyelonephritis/UTI: glucosuria provides a culture medium for <i>E. coli</i> and other bacteria</li> <li>Increased incidence of spontaneous abortion (in DM1 and DM2, not in GDM): related to pre-conception glycemic control</li> </ul>	<b>Labour and Delivery</b> <ul style="list-style-type: none"> <li>Preterm labour/prematurity: most commonly in patients with hypertension/preeclampsia. Preterm labour is associated with poor glycemic control but the exact mechanism is unknown</li> <li>Increased incidence of stillbirth</li> <li>Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia</li> </ul>
	<b>Neonatal</b> <ul style="list-style-type: none"> <li>Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate</li> <li>Hyperbilirubinemia and jaundice: due to prematurity and polycythemia</li> <li>Hypocalcemia: exact pathophysiology not understood, may be related to functional hypoparathyroidism</li> <li>Polycythemia: hyperglycemia stimulates fetal erythropoietin production</li> </ul>

## Hypertension in Pregnancy



- hypertensive disorders of pregnancy are classified as either **preexisting** or **gestational hypertension**

### PRE-EXISTING HYPERTENSION

#### Definition

- HTN (>140/90) prior to 20 wk GA, persisting >7 wk postpartum
- essential hypertension is associated with an increased risk of gestational HTN, abruptio placentae, IUGR and intrauterine fetal demise (IUFD)



**Ominous symptoms of HTN in pregnancy**  
RUQ pain, headache and visual disturbances.

### GESTATIONAL HYPERTENSION

#### Definition

- sBP >140 or dBP >90 developing after 20th wk GA in a woman known to be normotensive before pregnancy

#### Risk Factors

- maternal factors
  - primigravida (80-90% of gestational HTN)
  - first conception with a new partner
  - PMHx or FHx of gestational HTN
  - DM, chronic HTN, or renal insufficiency
  - Antiphospholipid syndrome
  - extremes of maternal age (<18 or >35 yr)
- fetal factors
  - IUGR or oligohydramnios, GTN, multiple gestation, fetal hydrops
  - previous stillbirth or intrauterine fetal demise

## Clinical Evaluation of Hypertension in Pregnancy

- in general, clinical evaluation should include the mother and fetus
- **evaluation of mother:**
  - body weight
  - central nervous system
    - ♦ presence and severity of headache
    - ♦ visual disturbances – blurring, scotomata
    - ♦ tremulousness, irritability, somnolence
    - ♦ hyperreflexia
  - hematologic
    - ♦ bleeding, petechiae
  - hepatic
    - ♦ RUQ or epigastric pain
    - ♦ severe nausea and vomiting
  - renal
    - ♦ urine output and colour
  - non-dependent edema (i.e. hands and face)
- **evaluation of fetus:**
  - fetal movement
  - fetal heart rate tracing – NST
  - ultrasound for growth
  - biophysical profile
  - Doppler flow studies

## Laboratory Evaluation of Gestational Hypertension

- hemoglobin, platelets, blood film
- PTT, INR, fibrinogen, D-dimer – especially if surgery or regional anesthetics are planned
- ALT, AST, LDH, bilirubin
- proteinuria, creatinine, uric acid
- 24 h urine collection for total protein and creatinine clearance

## Complications

- maternal
  - liver and renal dysfunction
  - seizure
  - abruptio placentae
  - left ventricular failure/pulmonary edema
  - DIC (release of placental thromboplastin consumptive coagulopathy)
  - HELLP syndrome (see Table 12, OB19)
    - ♦ treat with FFP infusion or plasma exchange
  - hemorrhagic stroke (50% of deaths)
- fetal (2° to placental insufficiency)
  - IUGR, prematurity, abruptio placentae, IUFD

## Management

- for both preexisting and gestational hypertension, labetalol 100-300 mg PO bid/tid, nifedipine, 30-50 mg PO daily or  $\alpha$ -methyldopa 250-500 mg PO tid/qid
- no ACE inhibitors, diuretics or propranolol (teratogens)
- preexisting HTN and gestational HTN without any deterioration can be followed until 37 wk then decide to induce shortly thereafter

## PREECLAMPSIA

### Definition

- pre-existing or gestational hypertension with new onset proteinuria or adverse conditions

### Risk Factors

- nulliparity
- preeclampsia in a previous pregnancy
- age >40 yr or <18 yr
- FHx of preeclampsia
- chronic HTN
- chronic renal disease
- antiphospholipid antibody syndrome or inherited thrombophilia
- vascular or connective tissue disease
- diabetes mellitus (pregestational and gestational)
- high BMI
- hydrops fetalis



### I-A Evidence-Recommendation Highlights of SOGC Clinical Practice Guidelines Diagnosis, Evaluation, and Management of the Hypertensive Disorders of Pregnancy

JOGC 2008;30:S1-47

- For BP measurement, Korotkoff phase V should be used to designate the dBP
- For preeclampsia prevention among low-risk women with low dietary calcium intake (<600 mg/d), oral calcium supplementation of at least 1g/d is recommended
- For preeclampsia prevention among increased risk women, low-dose Aspirin® (75-100 mg/d) is recommended until delivery
- Umbilical artery Doppler velocimetry should be part of the antenatal fetal surveillance in preeclampsia
- Initial antihypertensive therapy for severe hypertension (sBP >160 mmHg or dBP ≥110) should be with labetalol, nifedipine, or hydralazine
- Initial antihypertensive therapy for non-severe hypertension (BP 140-159/90-109 mmHg) should be with methyldopa,  $\beta$ -blockers, or calcium channel blockers
- Antenatal corticosteroids for fetal lung maturation should be considered for all women with preeclampsia before 34 wk gestation
- In a planned vaginal delivery with an unfavourable cervix, cervical ripening should be used
- Oxytocin 5 units IV or 10 units IM should be used as part of the management during the third stage of labour
- MgSO<sub>4</sub> is the recommended first-line treatment for eclampsia
- MgSO<sub>4</sub> is the recommended eclampsia prophylaxis in severe preeclampsia



### Hypertension in Pregnancy

#### Adverse Maternal Conditions

- sBP >160 mmHg
- dBP >100 mmHg
- HELLP
- Cerebral haemorrhage
- Renal dysfunction: oliguria <500 mL/d
- Left ventricular failure, pulmonary edema
- Abruptio, DIC

#### Symptoms:

- Abdominal pain, nausea, vomiting
- Headaches, visual problems
- SOB, chest pain
- Eclampsia: convulsions

#### Adverse Fetal Conditions

- Intrauterine growth restriction
- Oligohydramnios
- Absent/reversed umbilical artery end diastolic flow

#### Can result in:

- Fetal disability and/or death



- unexplained fetal growth restriction
- abruptio placentae
- there is a potential for further deterioration to severe preeclampsia as defined above (see Figure 3)
- the adverse conditions are many and include both maternal and fetal issues (see sidebar, OB15)

### Management

- management will depend on GA, possible threat of seizures (check reflexes)
- if stable and no adverse factors, may admit and follow, ± decide to deliver as approaching 34-36 wk (must weigh risks of fetal prematurity vs. risks of developing severe preeclampsia/eclampsia)
- for severe preeclampsia, stabilize and deliver
- if severe preeclampsia, during labour, increase maternal monitoring: hourly input and output, urine dip q12h, hourly neurological vitals, and increase fetal monitoring (continuous FHR monitoring)
- antihypertensive therapy
  - lowering BP decreases the risk of stroke
  - hydralazine 5-10 mg IV bolus over 5 min q15-30min as necessary
  - labetalol 20-50 mg IV q10min
  - 2nd line: nifedipine 10-20 mg PO q20-60min
- seizure prevention
  - MgSO<sub>4</sub>
  - postpartum management
  - risk of seizure highest in first 24 h postpartum – continue MgSO<sub>4</sub> for 12-24 h after delivery
  - vitals q1h
  - consider HELLP syndrome in toxic patients
  - most return to a normotensive BP within 2 wk



#### Preeclampsia Investigations

- CBC
- Liver enzymes
- INR and aPTT
- Cr
- Uric Acid
- LDH
- Albumin
- Bilirubin
- Urine (dip ± 24 h collection)



#### HELLP Syndrome

- Hemolysis
- Elevated Liver enzymes
- Low Platelets

## ECLAMPSIA

### Definition

- the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions

### Epidemiology

- an eclamptic seizure occurs in approximately 0.5% of mildly preeclamptic women and 2-3% of severely preeclamptic women

### Risk Factors

- same as risk factors for Preeclampsia, see above

### Clinical Manifestations

- eclampsia is a clinical diagnosis
- typically tonic-clonic and lasting 60-75 s
- one of the signs of an impending seizure is hyperreflexia
- symptoms that may occur before the seizure include persistent frontal or occipital headache, blurred vision, photophobia, right upper quadrant or epigastric pain, and altered mental status
- in up to one third of cases, there is no proteinuria or blood pressure is less than 140/90 mmHg prior to the seizure
- in general, women with typical eclamptic seizures who do not have focal neurologic deficits or prolonged coma do not require diagnostic evaluation including imaging

### Management

- ABCs
- roll patient into LLDP
- supplemental O<sub>2</sub> via face mask to treat hypoxemia due to hypoventilation during convulsive episode
- aggressive antihypertensive therapy for sustained diastolic pressures ≥105 mmHg or systolic blood pressures ≥160 mmHg with hydralazine or labetalol
- prevention of recurrent convulsions: to prevent further seizures and the possible complications of repeated seizure activity (e.g. rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, etc.) MgSO<sub>4</sub> is now the drug of choice, with previously used agents including diazepam and phenytoin
- the definitive treatment of eclampsia is DELIVERY, irrespective of gestational age, to reduce the risk of maternal morbidity and mortality from complications of the disease
- mode of delivery is dependent on clinical situation and fetal-maternal condition



#### Differential Diagnosis of Cause for Seizure in a Pregnant Woman

- Stroke
- Hypertensive disease (hypertensive encephalopathy, pheochromocytoma)
- Space-occupying lesion of the CNS
- Metabolic disorders (hypoglycemia, SIADH)
- Infection (meningitis, encephalitis)
- Thrombotic thrombocytopenic purpura or thrombophilia
- Idiopathic epilepsy
- Use of illicit drugs
- Cerebral vasculitis



#### Note

Eclampsia prior to 20 wk of gestation is rare and should raise the possibility of an underlying molar pregnancy or antiphospholipid syndrome.



#### MgSO<sub>4</sub> toxicity

- Flushing
- Hyporeflexia
- Somnolence
- Respiratory and cardiac depression
- Weakness

**Note:** Increased risk of toxicity with concurrent calcium channel blocker use or renal disease

#### Treatment:

- Stop MgSO<sub>4</sub>
- Calcium gluconate 10% in 10 mL via IV

## Nausea and Vomiting

### Epidemiology

- affects 50-90% of pregnant women
- often limited to T1 but may persist

### Management

- r/o other causes of N/V
- weigh frequently, assess level of hydration, test urine for ketones
- **non-pharmacological:**
  - avoid mixing fluids and solids, frequent small meals
  - stop prenatal vitamins (folic acid must continue until >12 wk)
  - increase sleep/rest
  - ginger (maximum 1000 mg/d)
  - acupuncture, acupressure
- **pharmacological:**
  - first line: Diclectin® (10 mg doxylamine succinate with vitamin B<sub>6</sub>) 4 tablets PO daily to maximum of 8 tablets
  - if no improvement, try dimenhydrinate (50-100 mg q4-6h PO), followed by hydroxyzine, pyridoxine, phenothiazine, or metoclopramide
  - vitamin B<sub>6</sub> lollipops
  - if patient dehydrated, assess fluid replacement needs and resuscitate accordingly
- **severe/refractory:**
  - consider homecare with IV fluids and parenteral anti-emetics, hospitalization

## Hyperemesis Gravidarum

### Definition

- intractable nausea and vomiting, usually presents in T1 then diminishes; occasionally persists throughout pregnancy
- affects ~1% of pregnancies

### Etiology

- multifactorial with hormonal, immunologic and psychologic components
- rapidly rising  $\beta$ -hCG  $\pm$  estrogen levels may be implicated

### Investigations

- r/o systemic causes: GI inflammation, pyelonephritis, thyrotoxicosis
- r/o obstetrical causes: multiple gestation, GTN, HELLP syndrome
- CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
- ultrasound

### Management

- thiamine supplementation may be indicated
- **non-pharmacological:** (see *Nausea and Vomiting*, above)
- **pharmacological options**
  - Diclectin® (see dosage *Nausea and Vomiting*, above)
  - Dimenhydrinate can be safely used as an adjunct to Diclectin® (1 suppository bid or 25 mg PO qid)
  - other adjuncts: hydroxyzine, pyridoxine, phenothiazine, metoclopramide
  - also consider: ondansetron or methylprednisolone
  - if severe: admit to hospital, NPO initially then small frequent meals, correct hypovolemia, electrolyte disturbance and ketosis, TPN (if very severe) to reverse catabolic state

### Complications

- maternal
  - dehydration, electrolyte and acid-base disturbances
  - Mallory-Weiss tear
  - Wernicke's encephalopathy, if protracted course
  - death
- fetal: usually none, IUGR is 15x more common in women losing >5% of pre-pregnancy weight



## Jaundice in Pregnancy

### Epidemiology

- affects 1 in 1500 pregnancies

### Etiology

- viral hepatitis (most common)
- unique to pregnancy (see Table 12)
- cholestatic jaundice of pregnancy
- HELLP syndrome
- hepatic rupture, hematoma and infarct
- AFLP
- hyperemesis gravidarum (rarely causes hepatic dysfunction)
- pre-existing conditions (see [Gastroenterology](#), *Liver/Biliary Tract*, G28, G40)



**Table 12. Conditions Causing Jaundice in Pregnancy**

	HELLP Syndrome	Cholestatic Jaundice of Pregnancy	Hepatic Infarct, Hematoma, and Rupture	Acute Fatty Liver of Pregnancy (AFLP)
<b>Definition</b>	Hemolysis, elevated liver enzymes, low platelets Pathogenesis unknown	Clinical syndrome characterized by intense pruritus that precedes jaundice by 7-14 d Pathogenesis unknown, may be due to increased sensitivity to high levels of estrogen or abnormal progesterational steroids	Rare consequence of preeclampsia, typically occurring in T3 Vasospasm-induced hepatic infarction can lead to hematoma formation; hematoma can lead to rupture	Form of hepatic failure with coagulopathy and encephalopathy characterized by microvesicular fatty infiltrates in liver parenchyma Pathogenesis unknown
<b>Epidemiology</b>	Affects 20% of women with severe preeclampsia Presents >27 wk GA (11% sooner); up to 30% of cases present AFTER delivery and with no previous signs of hypertension	17-29 wk GA High incidence in Chile and Scandinavia; rare in Asian and African populations		1 in 7,000 deliveries 3rd trimester (28-40 wk GA) Maternal mortality as high as 75%; resolution of hepatic dysfunction with delivery or termination of pregnancy
<b>Clinical Features</b>	Epigastric, RUQ or chest pain, N/V, symptoms of preeclampsia (headache, blurred vision, thirst) ± jaundice Atypical presentations: asymptomatic reduction in platelet count, "flu-like" symptoms	Intense pruritus (usually, worst on palms and soles of feet) ± icterus (1-2 wk later) Steatorrhea unusual	Hepatic rupture: RUQ abdominal pain, abdominal distention, nausea/vomiting, and hypertension, followed by shock	Acute nausea/vomiting, severe upper abdominal pain preceding jaundice Confusion Preeclampsia Pruritus Range in presentation: • Mild to fulminant
<b>Investigations</b>	AST (70-663 U/L), total bilirubin slightly increased, low platelet count (7-99), elevated LDH ± elevated D-dimers, tissue polypeptide antigen (TPA) and fibronectin, fragmented RBCs on smear Liver biopsy (rarely done)	ALT <500 IU, ALP and GGT markedly elevated (to levels consistent with moderate to severe cholestasis)	Hemoperitoneum (paracentesis, U/S, CT, MRI showing ruptured liver)	Elevated PTT and low serum fibrinogen AST > ALT Hypoglycemia Preeclampsia and HELLP features Liver biopsy to establish diagnosis • If liver biopsy not possible, CT most useful
<b>Management</b>	Supportive care (in ICU) and prompt delivery	Ursodeoxycholic acid (20-25 mg/kg/d) Pruritus: cholestyramine Prophylactic vitamin K before delivery Consider induction of labour (see <i>Induction of Labour</i> , OB36)	Aggressive: rapid delivery and trauma surgery to repair liver	Early diagnosis with prompt delivery followed by maximal supportive care • ABCs, mechanical ventilation, transfusion of blood products • Hepatic encephalopathy treatment: lactulose, catharsis • Treat hypoglycemia
<b>Notes</b>	Complications: sepsis, multi-system organ failure, hepatic failure, DIC, death (rare)	Selenium may be protective against cholestasis Strong familial predisposition Correlates with oral contraceptive sensitivity	Complications include death (mother and fetus) if untreated	Recovery begins with delivery Persistent or increasing hyperbilirubinemia and complications

## Urinary Tract Infection (UTI)



### Etiology

- increased urinary stasis from mechanical and hormonal (progesterone) factors
- organisms include GBS as well as those that occur in non-pregnant women

### Epidemiology

- most common medical complication of pregnancy
- asymptomatic bacteriuria in 2-7% of pregnant women, more frequently in multiparous women
- note: asymptomatic bacteriuria should be treated in pregnancy due to increased risk of pyelonephritis.



Treat asymptomatic bacteriuria in pregnancy because of increased risk of progression to cystitis, pyelonephritis and probable increased risk of PRETERM LABOUR.

### Clinical Features

- may be asymptomatic
- dysuria, urgency, and frequency in cystitis
- fever, flank pain, costovertebral angle tenderness in pyelonephritis

### Investigations

- urinalysis, urine C&S
- cystoscopy, and renal function tests in recurrent infections

### Management

- uncomplicated UTI
  - first line: amoxicillin (250-500 mg PO q8h x 7 d)
  - alternatives: nitrofurantoin (100 mg PO bid x 7 d)
  - follow with monthly urine cultures
- pyelonephritis
  - hospitalization and IV antibiotics

### Prognosis

- complications if untreated: acute cystitis, pyelonephritis, and possible PPRM
- recurrence is common



## Infections During Pregnancy



Table 13. Infections During Pregnancy

Infection	Agent	Source of Transmission	Greatest Transmission Risk to Fetus	Effects on Fetus	Effects on Mother	Diagnosis	Management
<b>Chicken Pox</b>	Varicella zoster virus (herpes family)	To mom: direct, respiratory To baby: transplacental	13-30 wk GA, and 5 d pre- to 2 d post-delivery	Congenital varicella syndrome (limb aplasia, chorioretinitis, cataracts, cutaneous scars, cortical atrophy, IUGR, hydrops), preterm labour (prematurity)	Fever, malaise, vesicular pruritic lesions	Clinical, $\pm$ vesicle fluid culture, $\pm$ serology	VZIG for mother if exposed, decreases congenital varicella syndrome Note: Do not administer vaccine during pregnancy (live attenuated)
<b>*CMV</b>	DNA virus (herpes family)	To mom: blood/organ transfusion, sexual contact To baby: transplacental, during delivery, breast milk	T1-T3	5-10% develop CNS involvement (mental retardation, cerebral calcification, hydrocephalus, microcephaly, deafness, chorioretinitis)	Asymptomatic or flu-like	Serologic screen; isolate virus from urine or secretion culture	No specific treatment; maintain good hygiene and avoid high risk situations
<b>Erythema Infectiosum (Fifth Disease)</b>	Parvovirus B19	To mom: respiratory, infected blood products To baby: transplacental	10-20 wk GA	Spontaneous abortion (SA), stillbirth, hydrops in utero	Flu-like, rash, arthritis; often asymptomatic	Serology, viral PCR, maternal AFP; if IgM present, follow fetus with U/S for hydrops	If hydrops occurs, consider fetal transfusion

Table 13. Infections During Pregnancy (continued)

Infection	Agent	Source of Transmission	Greatest Transmission Risk to Fetus	Effects on Fetus	Effects on Mother	Diagnosis	Management
<b>Hepatitis B</b>	DNA virus	To mom: blood, saliva, semen, vaginal secretions To baby: transplacental, breast milk	T3 10% vertical transmission if asymptomatic HBsAg +ve; 85-90% if HBsAg and HBeAg +ve	Prematurity, low birth weight, neonatal death	Fever, N/V, fatigue, jaundice, elevated liver enzymes	Serologic screening for all pregnancies	Rx neonate with HBIG and vaccine (at birth, 1, 6 mo); 90% effective
<b>*Herpes Simplex Virus</b>	DNA virus	To mom: intimate mucocutaneous contact To baby: transplacental, during delivery	Delivery (if genital lesions present); less commonly in utero	Disseminated herpes (20%); CNS sequelae (35%); self-limited infection	Painful vesicular lesions	Clinical diagnosis	Acyclovir for symptomatic women, suppressive therapy at 36 wk controversial C/S if active genital lesions, even if remote from vulva
<b>HIV</b>	RNA retrovirus	To mom: blood, semen, vaginal secretions To baby: in utero, during delivery, breast milk	1/3 in utero, 1/3 at delivery, 1/3 breastfeeding	IUGR, preterm labour, premature rupture of membranes	See <a href="#">Infectious Diseases</a> , ID41 	Serology, viral PCR All pregnant women are offered screening	Triple antiretroviral therapy decreases transmission to <1% Elective C/S: no previous antiviral Rx or monotherapy only, viral load unknown or >500 RNA copies/mL, unknown prenatal care, patient request
<b>*Rubella</b>	ssRNA togavirus	To mom: respiratory droplets (highly contagious) To baby: transplacental	T1	SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, MR, IUGR, hepatitis, CNS defects, osseous changes)	Rash (50%), fever, posterior auricular or occipital lymphadenopathy, arthralgia	Serologic testing; all pregnant women screened (immune if titre >1:16); infection if IgM present or >4x increase in IgG	No specific treatment; offer vaccine following pregnancy Do not administer during pregnancy (live attenuated)
<b>Syphilis</b>	Spirochete ( <i>Treponema pallidum</i> )	To mom: sexual contact To baby: transplacental	T1-T3	Risk of PTL, multisystem involvement, fetal death	See <a href="#">Infectious Diseases</a> , ID25 	VDRL screening for all pregnancies; if positive, requires confirmatory testing	Pen G 2.4 M U IM 1 dose if early syphilis 3 doses if late syphilis, monitor VDRL monthly If Pen G allergic: Clindamycin 900mg IV q8h
<b>*Toxoplasmosis</b>	Protozoa ( <i>Toxoplasma gondii</i> )	To mom: raw meat, unpasteurized goat's milk, cat feces/urine To baby: transplacental	T3 (but most severe if infected in T1); only concern if primary infection during pregnancy	Congenital toxoplasmosis (chorioretinitis, hydrocephaly, intracranial calcification, MR, microcephaly) NB: 75% initially asymptomatic at birth	Majority subclinical; may have flu-like symptoms	IgM and IgG serology; PCR of amniotic fluid	Self-limiting in mother; spiramycin decreases fetal morbidity but not rate of transmission

\* Indicates TORCH infection

## Venous Thromboembolism (VTE)



### Epidemiology

- incidence 0.5-3/1,000 pregnancies occurring with approximately equal frequency in all three trimesters and postpartum

### Risk Factors

- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, thrombophilias (see [Hematology](#), H31)



**Table 14. Risk Factors for VTE Specific to Pregnancy**

Hypercoagulability	Stasis	Endothelial
Increased factors: II, V, VII, VIII, IX, X, XII, fibrinogen Increased platelet aggregation Decreased protein S, tPA, factors XI, XIII	Increased resistance to activated protein C Antithrombin can be normal or reduced Increased venous distensibility Decreased venous tone 50% decrease in venous flow in lower extremity by T3 Uterus is mechanical impediment to venous return	Vascular damage at delivery (C/S or SVD) Uterine instrumentation Peripartum pelvic surgery

**Virchow's Triad for VTE**

- Hypercoagulable state
- Stasis
- Endothelial damage

**Clinical Features**

- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a pulmonary embolism are non-specific (as in non-pregnant women)
- unexplained spontaneous fetal loss

**Investigations**

- duplex venous Doppler sonography for DVT
- CXR and V/Q scan or Spiral CT for PE

**Management**

- before initiating treatment, obtain a baseline CBC, including platelets, and aPTT
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- unfractionated heparin
  - bolus of 5,000 IU followed by an infusion of ~30,000 IU/24h
  - measure aPTT 6 h after the bolus
  - maintain aPTT at a therapeutic level (1.5-2 x normal)
  - repeat q24h once therapeutic
  - heparin-induced thrombocytopenia (HIT) uncommon (3%) but serious complication
  - LMWH can also be used in pregnancy
- compression stockings
- poor evidence to support a recommendation for or against avoidance of prolonged sitting
- VTE prophylaxis:
  - women on long-term anticoagulation: full therapeutic anticoagulation throughout pregnancy and for 6-12 wk postpartum
  - women with a non-active PMHx of VTE: unfractionated heparin regimens suggested
- routine VTE prophylaxis:
  - insufficient evidence in pregnancy to recommend routine use of LMWH
  - current prophylaxis regimens for acquired thrombophilias (e.g. APS syndrome) include low dose Aspirin® in conjunction with prophylactic heparin

## Bleeding in Pregnancy

### First and Second Trimester Bleeding

**Approach to the Patient with Bleeding in T1/T2**

- **history**
  - risk factors for ectopic pregnancy (previous ectopic pregnancies, history of STI/PID, IUD use, previous pelvic surgery, smoking)
  - previous spontaneous abortion
  - recent trauma
  - characteristics of the bleeding (including any tissue passed)
  - characteristics of the pain (cramping pain suggests SA)
  - history of coagulopathy
  - gynecological/obstetric history
  - dizziness (significant blood loss, may be associated with ruptured ectopic)
  - fever (may be associated with septic abortion)
- **physical**
  - vitals (including orthostatic changes)
  - abdomen (SFH, tenderness, presence of contractions)
  - perineum (signs of trauma, genital lesions)
  - speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
  - pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness)

**Bleeding in Pregnancy Definitions**

- First trimester bleeding: vaginal bleeding within the first 12 wk
- Second trimester bleeding: <20 wk

**Differential Diagnosis**

- Physiologic bleeding: spotting, due to implantation of placenta – reassure and check serial  $\beta$ -hCGs
- Abortion (threatened, inevitable, incomplete, complete) (see Table 15)
- Abnormal pregnancy (ectopic, molar) (see [Gynecology](#), *Hydatidiform Mole* G48)
- Trauma (post-coital or after pelvic exam)
- Genital lesion (e.g. cervical polyp, neoplasms)

### Investigations

- $\beta$ -hCG (lower than expected for GA in spontaneous abortion (SA), ectopic pregnancy)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

### Treatment

- IV resuscitation for hemorrhagic shock
- treat the underlying cause

## Spontaneous Abortions

- see *Termination of Pregnancy*, OB11 for therapeutic abortions

**Table 15. Classifications of Spontaneous Abortions**

Type	History	Clinical	Management ( $\pm$ Rhogam <sup>®</sup> )
<b>Threatened</b>	Vaginal bleeding $\pm$ cramping	Cervix closed and soft U/S shows viable fetus	Watch and wait <5% go on to abort
<b>Inevitable</b>	Increasing bleeding and cramps $\pm$ rupture of membranes	Cervix closed until products start to expel, then external os opens U/S variable but usually nonviable fetus	a) Watch and wait b) Misoprostol 400-800 $\mu$ g PO/PV c) D&C $\pm$ oxytocin
<b>Incomplete</b>	Extremely heavy bleeding and cramps $\pm$ passage of tissue noticed	Cervix open U/S products of conception	a) Watch and wait b) Misoprostol 400-800 $\mu$ g PO/PV c) D&C $\pm$ oxytocin
<b>Complete</b>	Bleeding and complete passage of sac and placenta	Cervix open U/S no products of conception	No D&C – expectant management
<b>Missed</b>	No bleeding (fetal death in utero)	Cervix closed U/S may show SGA, no fetal heart activity; nonviable fetus	a) Watch and wait b) Misoprostol 400-800 $\mu$ g PO/PV c) D&C $\pm$ oxytocin
<b>Recurrent</b>	3+ consecutive spontaneous abortions		Evaluate mechanical, genetic, environmental and other risk factors
<b>Septic</b>	Contents of uterus infected – infrequent		D&C IV broad spectrum antibiotics



### Etiology of Recurrent Pregnancy Loss

#### MAKE ME

Type	History
<b>Mechanical</b>	Uterine anomalies <ul style="list-style-type: none"> <li>• Congenital (septate uterus)</li> <li>• Leiomyoma</li> <li>• Endometrial polyps</li> <li>• Intrauterine adhesions</li> </ul>
<b>Autoimmune</b>	Immunologic Factors <ul style="list-style-type: none"> <li>• Antiphospholipid syndrome (blood tests: lupus anticoagulant, anti-cardiolipin Ab, anti-<math>\beta</math>2 glycoprotein-I)</li> </ul>
<b>Karyotype</b>	<ul style="list-style-type: none"> <li>• Aneuploidy</li> <li>• Chromosomal rearrangements</li> <li>• Check both parents</li> <li>• Young mother, <math>\geq 3</math> miscarriages, Fhx miscarriage/stillbirth/malformation</li> </ul>
<b>Endocrine</b>	Poorly controlled disease: <ul style="list-style-type: none"> <li>• Thyroid (associated with high antibody/hormone levels)</li> <li>• Diabetes mellitus (secondary to hyperglycemia, maternal vascular disease)</li> <li>• PCOS</li> </ul>
<b>Maternal Infection</b>	No infectious agent has been proven to cause recurrent pregnancy loss, though some cause sporadic loss (Listeria, toxoplasmosis, CMV, HSV)
<b>Environment</b>	Obesity, smoking, alcohol use, and caffeine consumption may contribute



### Management of Abortions

- Always rule out an ectopic
- Always check Rh; if negative, give Rhogam<sup>®</sup>
- Always ensure patient is hemodynamically stable



### Clinical Features of Ectopic Pregnancy

#### 4Ts and 1S

**Temperature**  $>38^{\circ}\text{C}$  (20%)

**Tenderness:** abdominal (90%)  $\pm$  rebound (45%)

**Tenderness** on bimanual examination, cervical motion tenderness

**Tissue:** palpable adnexal mass (50%) (half have contralateral mass due to lutein cyst)

**Signs of pregnancy** (e.g. Chadwick's sign, Hegar's sign)



More than half of patients with ectopic pregnancy have no risk factors.

## Ectopic Pregnancy



### Definition

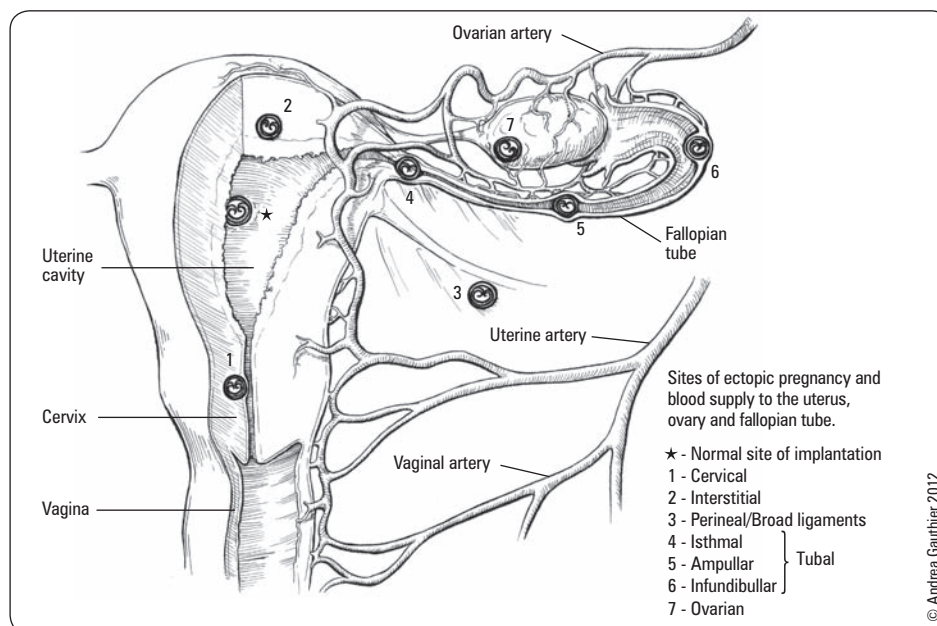
- embryo implants outside of the endometrial cavity

### Epidemiology

- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

### Etiology

- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube



**Figure 3. Sites of ectopic pregnancy implantation**

**Ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1)**

### Risk Factors

- previous ectopic pregnancy
- gynecologic:
  - IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with *C. trachomatis*), salpingitis
  - infertility
  - clomiphene citrate (for induction of ovulation)
- previous procedures:
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
  - IVF pregnancies following ovulation induction (7% ectopic rate)
- smoking
- structural:
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

### Investigations

- serial  $\beta$ -hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
  - rise of <20% of  $\beta$ -hCG is 100% predictive of a nonviable pregnancy
  - prolonged doubling time, plateau or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
  - 85% of ectopic pregnancies demonstrate abnormal  $\beta$ -HCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - intrauterine sac should be visible when serum  $\beta$ -hCG is
    - ♦ >1,500 mIU/mL (transvaginal)
    - ♦ >6,000 mIU/mL or 6 wk GA (transabdominal)
  - specific finding on transvaginal U/S is a tubal ring
- laparoscopy (for definitive diagnosis)

### Treatment

- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical (laparoscopy)
  - linear salpingostomy if tube salvageable
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
  - 15% risk of persistent trophoblast; must monitor  $\beta$ -hCG titres weekly until they reach non-detectable levels
  - consider Rhogam® if Rh negative
  - may require laparotomy if patient is unstable, extensive abdominal surgical history, etc.



#### DDx of Lower Abdominal Pain

- Urinary tract: UTI, kidney stones
- GI: diverticulitis, appendicitis
- Gyn: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related



#### If Ectopic Pregnancy Ruptures

- Acute abdomen with increasing pain
- Abdominal distention
- Shock



- medical = methotrexate (for indications see Figure 4)
  - use 50 mg/m<sup>2</sup> body surface area; given in a single IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)
  - follow  $\beta$ -hCG levels weekly until  $\beta$ -hCG is non-detectable
    - ♦ plateau or rising levels suggest persisting trophoblastic tissue (requires further treatment)
  - 82-95% success rate up to 25% will require a second dose
  - tubal patency following methotrexate treatment approaches 80%

### Prognosis

- 9% of maternal deaths during pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

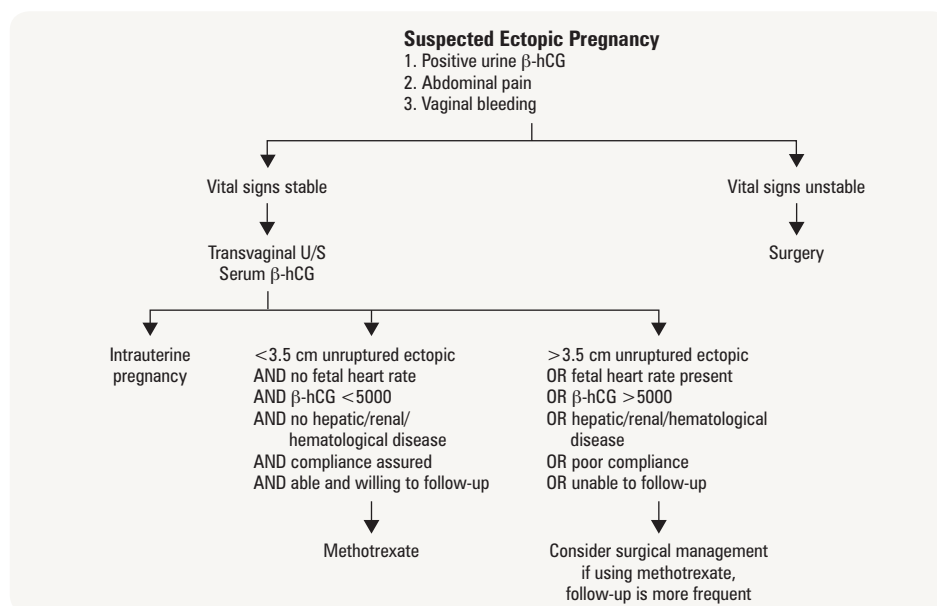


Figure 4. Algorithm for suspected ectopic pregnancy



### Interventions for Tubal Ectopic Pregnancy

Cochrane DB Syst Rev 2007;1:CD000324

**Study:** Cochrane Review of randomized controlled trials comparing treatments in women with tubal ectopic pregnancy.

**Patients:** Women with a diagnosis of tubal ectopic pregnancy.

**Intervention:** Surgery-salpingectomy/salpingostomy by open surgery or by laparoscopy, medical treatment, and expectant management.

**Main outcome:** Primary treatment success, defined as an uneventful decline in serum  $\beta$ -hCG to undetectable levels by the initial treatment.

**Results:** Intramuscular MTX therapy and salpingostomy yielded similar treatment success rates (82-95% for MTX therapy vs. 80-92% for salpingostomy).



## Antepartum Hemorrhage

### Definition

- vaginal bleeding from 20 wk to term

### Differential Diagnosis

- bloody show (shedding of cervical mucous plug) – most common etiology in T3
- placenta previa
- abruptio placentae – most common pathological etiology in T3
- vasa previa
- cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
- uterine rupture
- other: bleeding from bowel or bladder, placenta accreta, abnormal coagulation



### Key Questions to Ask in Antepartum Hemorrhage

- How much bleeding?
- Are there contractions/cramping/pain?
- Description? Colour, clotting, etc.

Table 16. Comparison of Placenta Previa versus Abruptio Placentae

	Placenta Previa	Abruptio Placentae
<b>Definition</b>	Abnormal location of the placenta near, partially or completely over the internal cervical os	Premature separation of a normally implanted placenta after 20 wk GA
<b>Etiology</b>	Idiopathic	Idiopathic
<b>Epidemiology</b>	0.5-0.8% of all pregnancies	1-2% of all pregnancies
<b>Risk factors</b>	<ul style="list-style-type: none"> <li>• History of placenta previa (4-8% recurrence risk)</li> <li>• Multiparity</li> <li>• Increased maternal age</li> <li>• Multiple gestation</li> <li>• Uterine tumour (e.g. fibroids) or other uterine anomalies</li> <li>• Uterine scar due to previous abortion, C/S, D&amp;C, myomectomy</li> </ul>	<ul style="list-style-type: none"> <li>• Previous abortion (recurrence rate 5-16%)</li> <li>• Maternal hypertension (chronic or gestational hypertension in 50% of abruptions) or vascular disease</li> <li>• Cigarette smoking (&gt;1 pack/d), excessive alcohol consumption, cocaine</li> <li>• Multiparity and/or maternal age &gt;35</li> <li>• PPRM</li> <li>• Rapid decompression of a distended uterus (polyhydramnios, multiple gestation)</li> <li>• Uterine anomaly, fibroids</li> <li>• Trauma (e.g. motor vehicle collision, maternal battery)</li> </ul>
<b>Bleeding</b>	PAINLESS	PAINFUL



### Levels of Abnormal Placental Invasion:

**Placenta Accreta:** AT myometrium (most common)

**Placenta Increta:** INTO myometrium

**Placenta Percreta:** PASSES through myometrium

## Placenta Previa



### Definition

- placenta implanted in the lower segment of the uterus, presenting ahead of the leading pole of the fetus
- the distance of the placental edge from the internal os is described in “millimeters away” from the internal os or “millimeters of overlap” over the internal os.
- greater than 20 millimeters of overlap over the internal os in the third trimester of pregnancy is highly predictive of the need for a C section.
- any degree of overlap after 35 wk is an indication for a C section

### Clinical Features

- PAINLESS bright red vaginal bleeding (recurrent), may be minimized and cease spontaneously, but can become catastrophic
- mean onset of bleeding is 30 wk GA, but onset depends on degree of previa
- **physical exam**
  - uterus soft and non-tender
  - presenting fetal part high or displaced
  - FHR usually normal
  - shock/anemia correspond to degree of apparent blood loss
- **complications**
  - fetal
    - ♦ perinatal mortality low but still higher than with a normal pregnancy
    - ♦ prematurity (bleeding often dictates early C/S)
    - ♦ intrauterine hypoxia (acute or IUGR)
    - ♦ fetal malpresentation
    - ♦ PPROM
    - ♦ risk of fetal blood loss from placenta, especially if incised during C/S
  - maternal
    - ♦ <1% maternal mortality
    - ♦ hemorrhage and hypovolemic shock, anemia, acute renal failure, pituitary necrosis (Sheehan syndrome)
    - ♦ placenta accreta – especially if previous uterine surgery, anterior placenta previa
    - ♦ hysterectomy



Do NOT perform a vaginal exam until placenta previa has been ruled out by U/S.

### Investigations

- transvaginal U/S is more accurate than transabdominal U/S at diagnosing placenta previa at any gestational age
- if the placenta lies between 20 mm of overlap and 20 mm away from the internal os after 26 wk regular transvaginal ultrasounds should be repeated at regular intervals – continued change in the placental location is likely.



**Kleihauer-Betke Test**  
Quantifies fetal cells in the maternal circulation.

### Management

- goal: keep pregnancy intrauterine until the risk of delivery < risk of continuing pregnancy
- stabilize and monitor
  - maternal stabilization: large bore IV with hydration, O<sub>2</sub> for hypotensive patients
  - maternal monitoring: vitals, urine output, blood loss, bloodwork (hematocrit, CBC, INR/PTT, platelets, fibrinogen, FDP, type and cross match)
  - electronic fetal monitoring
  - U/S assessment: when fetal and maternal condition permit, determine fetal viability, gestational age and placental status/position
- Rhogam® if mother is Rh negative
  - Kleihauer-Betke test to determine extent of fetomaternal transfusion so that appropriate dose of Rhogam® can be given
- GA <37 wk and minimal bleeding: expectant management
  - admit to hospital
  - limited physical activity, no douches, enemas, or sexual intercourse
  - consider corticosteroids for fetal lung maturity
  - delivery when fetus is mature or hemorrhage dictates
- GA ≥37 wk, profuse bleeding or L/S ratio is >2:1: deliver by C/S

## Abruptio Placentae



### Clinical Features

- **classification**
  - total (fetal death inevitable) vs. partial
  - external/revealed/apparent: blood dissects downward toward cervix
  - internal/concealed (20%): blood dissects upward toward fetus
  - most are mixed
- **presentation**
  - **PAINFUL** (80%) vaginal bleeding (bleeding not always present if abruption is concealed), uterine tenderness, uterine contractions
  - pain: sudden onset, constant, localized to lower back and uterus
  - shock/anemia out of proportion to apparent blood loss
  - $\pm$  fetal distress, fetal demise (15% present with demise), bloody amniotic fluid (fetal presentation typically normal)
  - $\pm$  coagulopathy

### Complications

- fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
- maternal complications:  $<1\%$  maternal mortality, DIC (in 20% of abruptions), acute renal failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), amniotic fluid embolus



Abruptio placentae is the most common cause of DIC in pregnancy.

### Investigations

- clinical diagnosis, U/S not sensitive for diagnosing abruption (sensitivity = 15%)

### Management

- maternal stabilization: large bore IV with hydration; O<sub>2</sub> for hypotensive patients
- maternal monitoring: vitals, urine output, blood loss, bloodwork (hematocrit, CBC, PTT/PT, platelets, fibrinogen, FDP, type and cross match)
- EFM
- blood products on hand (red cells, platelets, cryoprecipitate) because of DIC risk
- Rhogam® if Rh negative
  - Kleihauer-Betke test may confirm abruption
- mild abruption:
  - GA  $<37$  wk: use serial Hct to assess concealed bleeding, deliver when fetus is mature or when hemorrhage dictates
  - GA  $\geq 37$  wk: stabilize and deliver
- moderate to severe abruption:
  - hydrate and restore blood loss and correct coagulation defect if present
  - vaginal delivery if no contraindication and no evidence of fetal or maternal distress OR fetal demise
  - C/S if live fetus and fetal or maternal distress develops with fluid/blood replacement, labour fails to progress or if vaginal delivery otherwise contraindicated

## Vasa Previa

### Definition

- unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord into membranes of placenta or succenturiate (accessory) lobe

### Epidemiology

- 1 in 5,000 deliveries – higher in twin pregnancies

### Clinical Features

- **PAINLESS** vaginal bleeding and fetal distress (tachy- to bradyarrhythmia)
- 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of exsanguination)

### Investigations

- **Apt test** (NaOH mixed with the blood) can be done immediately to determine if the source of bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
- **Wright stain** on blood smear and look for nucleated red blood cells (in cord, not maternal blood)

### Management

- emergency C/S (since bleeding is from fetus, a small amount of blood loss can have catastrophic consequences)

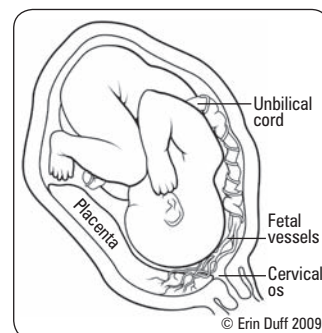


Figure 5. Vasa previa

# Multiple Gestation



## Epidemiology

- incidence of twins is 1/80 and triplets 1/6,400 in North America
- 2/3 of twins are dizygotic (fraternal)
  - risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, ethnicity (e.g. certain African regions)
- monozygous twinning occurs at a constant rate worldwide (1/250)
- determine zygosity by number of placentas, thickness of membranes, sex, blood type

## Clinical Features

Table 17. Complications Associated with Multiple Gestation

Maternal	Utero-placental	Fetal
Hyperemesis gravidarum	Increased PROM/PTL	Prematurity*
GDM	Polyhydramnios	IUGR
Gestational HTN	Placenta previa	Malpresentation
Anemia	Placental abruption	Congenital anomalies
Increased physiological stress on all systems	PPH (uterine atony)	Twin-twin transfusion
Increased compressive symptoms	Umbilical cord prolapse	Increased perinatal morbidity and mortality
C/S	Cord anomalies	Twin interlocking
	(velamentous insertion, 2 vessel cord)	(twin A breech, twin B vertex)
		Single fetal demise

\*Most common cause of perinatal mortality in multiple gestation

## Management

- U/S determination of chorionicity must be done within first trimester (ideally 8-12 wk GA)
- increased antenatal surveillance
  - serial U/S q2-3wk from 28 wk GA to assess growth (uncomplicated diamniotic dichorionic)
  - increased frequency of ultrasounds in monochorionic diamniotic and monochorionic monoamniotic twins
  - Doppler flow studies weekly if discordant fetal growth (>30%)
  - BPP as needed
- may attempt vaginal delivery if twin A presents as vertex, otherwise C/S (40-50% of all twin deliveries, 15% of cases have twin A delivered vaginally and twin B delivered by C/S)
- mode of delivery depends on fetal weight, GA, presentation



### The Ps of Multiple Gestation Complications

#### Increased rates of:

- Puking
- Pallor (anemia)
- Preeclampsia/PIH
- Pressure (compressive symptoms)
- PTL/PROM/PPROM
- Polyhydramnios
- Placenta previa/abruptio
- PPH/APH
- Prolonged labour
- Cord Prolapse
- Prematurity
- Mal Presentation
- Perinatal morbidity and mortality
- Parental distress
- Postpartum depression

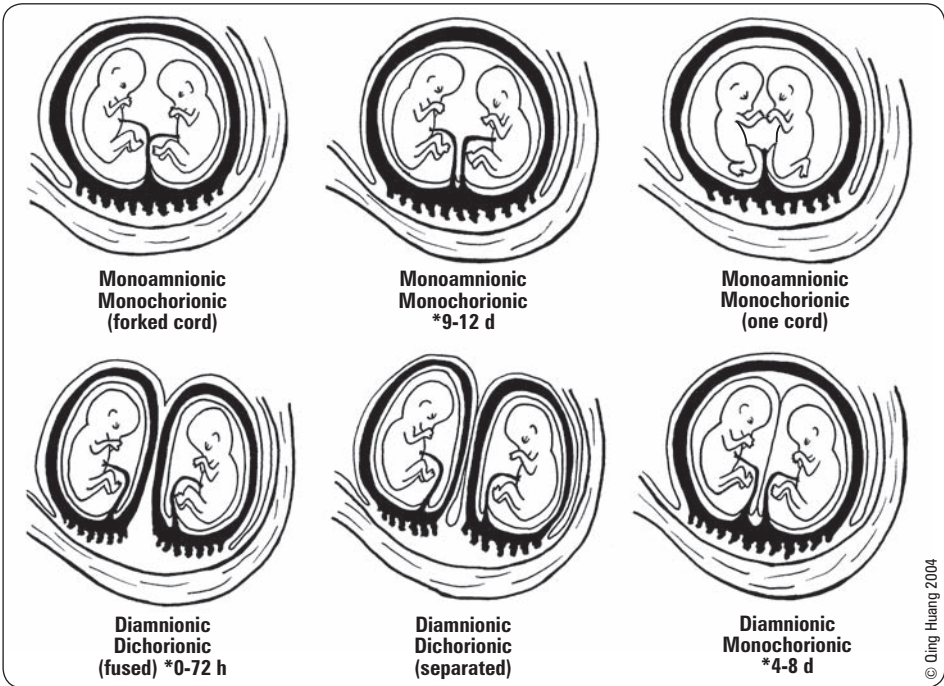


Figure 6. Classification of twin pregnancies

\*Indicates time of cleavage

## Twin-Twin Transfusion Syndrome

### Epidemiology

- 10% of monochorionic twins
- concern if >30% discordance in estimated fetal weight

### Etiology

- arterial blood from donor twin passes through placenta into vein of recipient twin

### Clinical Features

- donor twin: IUGR, hypovolemia, hypotension, anemia, oligohydramnios
- recipient twin: hypervolemia, hypertension, CHF, polycythemia, edema, polyhydramnios, kernicterus in neonatal period

### Investigations

- detected by U/S screening, Doppler flow analysis

### Management

- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary
- laparoscopic occlusion of placental vessels

## Growth Discrepancies



### Intrauterine Growth Restriction

#### Definition

- infant weight <10th percentile for GA or <2,500 g

#### Etiology/Risk Factors

- maternal causes
  - malnutrition, smoking, drug abuse, alcoholism, cyanotic heart disease, Type 1 DM, SLE, pulmonary insufficiency, previous IUGR
- maternal-fetal
  - any disease causing placental insufficiency
  - includes gestational HTN, chronic HTN, chronic renal insufficiency, gross placental morphological abnormalities (infarction, hemangiomas)
- fetal causes:
  - TORCH infections, multiple gestation, congenital anomalies

#### Clinical Features

- symmetric/Type I (20%): occurs early in pregnancy
  - inadequate growth of head and body
  - head:abdomen ratio may be normal (>1 up to 32 wk; =1 at 32-34 wk; <1 after 34 wk GA)
  - usually associated with congenital anomalies or TORCH infections
- asymmetric/Type II (80%): occurs late in pregnancy
  - brain is spared, therefore head:abdomen ratio increased
  - usually associated with placental insufficiency
  - more favorable prognosis than Type I
- complications
  - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, and mental retardation
  - greater risk of perinatal morbidity and mortality

#### Investigations

- SFH measurements at every antepartum visit
- if mother at high risk or SFH lags >2 cm behind GA:
  - anatomy U/S for BPD, head and abdominal circumference, femur length and fetal weight, AFW (decrease associated with IUGR)
  - $\pm$  BPP
  - Doppler analysis of umbilical cord blood flow

#### Management

- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition and treat maternal illness
- bed rest in LLDP
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if GA >34 wk
- liberal use of C/S since IUGR fetus withstands labour poorly



#### TORCH

Toxoplasmosis

Others: e.g. syphilis

Rubella

CMV

HSV

- See Table 13, OB20



#### Differential Diagnosis of

#### Incorrect Uterine Size for Dates

- Inaccurate dates
- Maternal: diabetes mellitus
- Maternal-fetal: polyhydramnios, oligohydramnios
- Fetal: abnormal karyotype, IUGR, macrosomia, fetal anomaly, abnormal lie, multiple gestation



#### Monitoring Fetal Growth with U/S

Done biweekly to show growth beyond the margin of error.

## Macrosomia

### Definition

- infant weight >90th percentile for a particular GA or >4,000 g

### Etiology/Risk Factors

- maternal obesity, GDM, past history of macrosomic infant, prolonged gestation, multiparity

### Clinical Features

- increased risk of perinatal mortality
- CPD and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labour (see *Medical Conditions in Pregnancy*, OB13)

### Investigations

- serial SFH
- further investigations if mother at high risk or SFH >2 cm ahead of GA
- U/S predictors
  - polyhydramnios
  - third trimester AC >1.5 cm/wk
  - HC/AC ratio <10th percentile
  - FL/AC ratio <20th percentile

### Management

- prophylactic C/S is a reasonable option where EFW >5,000 g in non-diabetic woman and EFW >4,500 g in diabetic woman
  - no evidence that prophylactic C/S improves outcomes
- early induction of labour is not recommended for non-diabetic mothers
- risks and benefits of early induction (risk of C/S vs. risk of dystocia) must be weighed in diabetic mothers, as current research is unclear

## Polyhydramnios/Oligohydramnios

Table 18. Polyhydramnios and Oligohydramnios

	Polyhydramnios	Oligohydramnios
<b>Definition</b>	AFI >25 cm U/S: single deepest pocket >8 cm	AFI <5 cm U/S: single deepest pocket ≤2 cm
<b>Etiology</b>	Idiopathic most common Maternal: <ul style="list-style-type: none"> <li>• Type 1 DM: abnormalities of transchorionic flow</li> </ul> Maternal-fetal: <ul style="list-style-type: none"> <li>• Chorioangiomas</li> <li>• Multiple gestation</li> <li>• Fetal hydrops (increased erythroblastosis)</li> </ul> Fetal: <ul style="list-style-type: none"> <li>• Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios)</li> <li>• Respiratory: cystic adenomatoid malformed lung</li> <li>• CNS: anencephaly, hydrocephalus, meningocele</li> <li>• GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfere with swallowing)</li> </ul>	Idiopathic most common Maternal: <ul style="list-style-type: none"> <li>• Uteroplacental insufficiency (pre-eclampsia, nephropathy)</li> <li>• Medications (ACEI)</li> </ul> Fetal: <ul style="list-style-type: none"> <li>• Congenital urinary tract anomalies (renal agenesis, obstruction, posterior urethral valves)</li> <li>• Demise/chronic hypoxemia (blood shunt away from kidneys to perfuse brain)</li> <li>• IUGR</li> <li>• Ruptured membranes: prolonged amniotic fluid leak</li> <li>• Amniotic fluid normally decreases after 35 wk</li> <li>• Post-dates (AFV normally decreases after 35 wk)</li> </ul>
<b>Epidemiology</b>	Occur in 0.2 to 1.6% of all pregnancies	Occur in ~4.5% of all pregnancies Severe form in <0.7% Common in pregnancies >41 wk (~12%)
<b>Clinical Features and Complications</b>	Uterus large for dates, difficulty palpating fetal parts and hearing FHR Maternal complications: <ul style="list-style-type: none"> <li>• Pressure symptoms from overdistended uterus (dyspnea, edema, hydronephrosis)</li> </ul> Obstetrical complications: <ul style="list-style-type: none"> <li>• Cord prolapse, placental abruption, malpresentation, preterm labour, uterine dysfunction and PPH</li> </ul>	Uterus small for dates Fetal complications: <ul style="list-style-type: none"> <li>• 15-25% have fetal anomalies</li> <li>• Amniotic fluid bands (T1) can lead to Potter's facies, limb deformities, abdominal wall defects</li> </ul> Obstetrical complications: <ul style="list-style-type: none"> <li>• Cord compression</li> <li>• Increased risk of adverse fetal outcomes</li> <li>• Pulmonary hypoplasia (late-onset)</li> <li>• Marker for infants who may not tolerate labour well</li> </ul>



**Table 18. Polyhydramnios and Oligohydramnios (continued)**

	Polyhydramnios	Oligohydramnios
<b>Management</b>	Determine underlying cause: <ul style="list-style-type: none"> <li>• Screen for maternal disease/infection</li> <li>• Complete fetal U/S evaluation</li> </ul> Depends on severity: <ul style="list-style-type: none"> <li>• Mild to moderate cases require no treatment</li> <li>• If severe, hospitalize and consider therapeutic amniocentesis</li> </ul>	Always warrants admission and investigation: <ul style="list-style-type: none"> <li>• R/O ROM</li> <li>• Fetal monitoring (NST, BPP)</li> <li>• U/S Doppler studies (umbilical cord and uterine artery)</li> </ul> Maternal hydration with oral or IV fluids to help increase amniotic fluid Vesicoamniotic shunt: if etiology is related to fetal obstructive uropathy; however, pulmonary function may not be restored with restoration of amniotic fluid Injection of fluid via amniocentesis will improve condition for ~1 wk – may be most helpful for visualizing any associated fetal anomalies Consider delivery if term Amnio-infusion may be considered during labour via intra-uterine catheter
<b>Prognosis</b>	2-5 fold increase in risk of perinatal mortality	Poorer with early onset High mortality related to congenital malformations and pulmonary hypoplasia when diagnosed during T2

## Normal Labour and Delivery

### Definition of Labour

- true labour: regular, painful contractions of increasing intensity associated with progressive **dilatation** and **effacement** of cervix and descent of presenting part, or progression of station
  - preterm (>20 but <36+6 wk GA)
  - term (37-41+6 wk GA)
  - post-term (>42 wk GA)
- false labour: Braxton-Hicks contractions
  - irregular contractions, with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any dilatation, effacement or descent
  - often relieved by rest or sedation

### The Cervix

- dilatation: latent phase: 0-3 cm; active phase: 4-10 cm
- effacement: thinning of the cervix by percentage or length of cervix (cm)
- consistency: firm vs. soft
- position: posterior vs. anterior
- application: contact between the cervix and presenting part (i.e. well or poorly applied)
- see Bishop score (Table 23, OB36)

### The Fetus

- **fetal lie**
  - orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, oblique)
- **fetal presentation**
  - fetal part presenting at pelvic outlet
    - ♦ breech (complete, frank, footling) (see Figure 9, OB40)
    - ♦ cephalic (vertex, face, asynclitic)
    - ♦ transverse (shoulder)
    - ♦ compound (fetal extremity prolapses along with presenting part)
  - all except vertex are considered malpresentations (see *High Risk Labour and Delivery*, OB38)
- **fetal position**
  - position of presenting part of the fetus relative to the maternal pelvis
    - ♦ OA: most common presentation (“normal”) – left OA most common
    - ♦ OP: most rotate spontaneously to OA; may cause prolonged second stage of labour
    - ♦ OT: leads to arrest of dilatation
  - normally, fetal head enters maternal pelvis and engages in OT position
  - subsequently rotates to OA position (or OP in a small percentage of cases)



#### Maternal Triage Assessment

**ID:** Age, GPA, EDD, GA, GBS, Rh, Ser

**CC**

**HPI:** 4 key questions:

- Contractions: Since when, how close (q x min), how long (x s), how painful
- Bleeding: Since when, how much (pads), colour (pink/mucous = show vs. brownish vs. bright red ± clots), pain?, last U/S, trauma/intercourse?
- Fluid (ROM): Since when, large gush vs. trickle, soaked pants?, clear vs. green vs. red?, continuous?
- FM: As much as usual?, When last movement?, Kick counts (lie still for 1-2 h, cold juice, feel FM – should have 6 movements in 2 h)

**HxPreg:** Any complications (HTN, GDM, infections), IPS/FTS screening, last ultrasound (BPP score, growth/estimated fetal weight, position), last vaginal exam

**POBHx:** Every previous pregnancy and outcome: Year, SVD/CS/miscarriage/abortion, baby size, length of labour, use of vacuum or forceps, complications

**PMHx, Meds, Allergies, SHx**

**O/E:** Maternal vitals, fetal heart tracing (baseline, variability, presence of accelerations/decelerations), Leopold's, vaginal exam, U/S



#### Reference point for describing fetal position:

- Occiput for cephalic presentation
- Sacrum for breech presentation
- Mentum for face presentation

- **attitude**
  - flexion/extension of fetal head relative to shoulders
    - ♦ brow presentation: head partially extended (requires C/S)
    - ♦ face presentation: head fully extended
      - mentum posterior always requires C/S, mentum anterior will deliver vaginally
- **station**
  - position of presenting part relative to ischial spines – determined by vaginal exam
    - ♦ at ischial spines = station 0 = engaged
    - ♦ -5 to -1 cm above ischial spines or
    - ♦ +1 to +5 cm below ischial spines
    - ♦ alternatively stations can be placed on a scale from -3 to +3

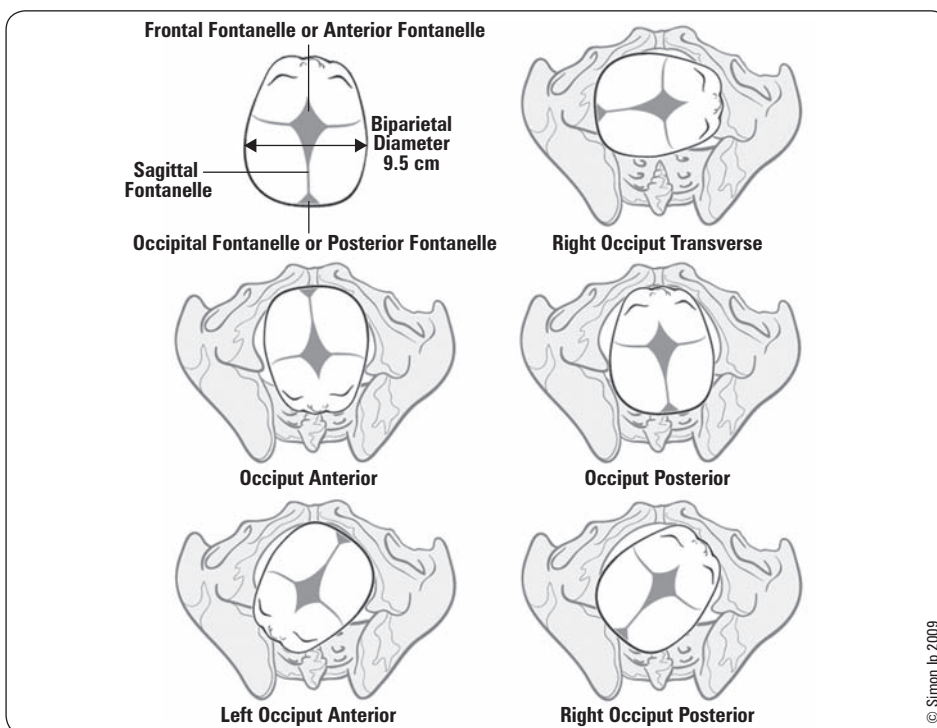


Figure 7. Fetal positions

## Four Stages of Labour

### First Stage of Labour

- latent phase
  - uterine contractions typically infrequent and irregular
  - slow cervical dilatation (usually to 3-4 cm) and effacement
- active phase
  - rapid cervical dilatation to full dilatation (nulliparous ~1.2 cm/h, multiparous ~1.5 cm/h)
  - phase of maximum slope on cervical dilatation curve (see Figure 10, OB43)
  - painful, regular contractions q2-3 min, lasting 45-60 s
  - contractions strongest at fundus, weakest at lower segment

### Second Stage of Labour

- from full dilatation to delivery of the baby
- mother feels a desire to bear down and push with each contraction
- women may choose a comfortable position that enhances pushing efforts and delivery
  - upright (semi-sitting, squatting) and LLDP are supported in the literature
- progress measured by descent

### Third Stage of Labour

- separation and expulsion of the placenta
- can last up to 30 min before intervention indicated
- start oxytocin IV drip or give 10 U IM after delivery of anterior shoulder in anticipation of placental delivery, otherwise give after delivery of placenta
- routine oxytocin administration in third stage of labour can reduce the risk of PPH by >40%



#### Course of Normal Labour

Stage	Nulliparous	Multiparous
First	6-18 h	2-10 h
Second	30 min-3 h	5-30 min
Third	5-30 min	5-30 min



#### Signs of Placental Separation

- Gush of blood
- Lengthening of cord
- Uterus becomes globular
- Fundus rises



#### Continuous Support for Women During Childbirth

Cochrane DB Syst Rev 2011;16:CD003766

**Study:** Systematic review of 21 RCTs from 11 countries, 15,061 women in labour.

**Intervention:** Continuous support during labour vs. usual care.

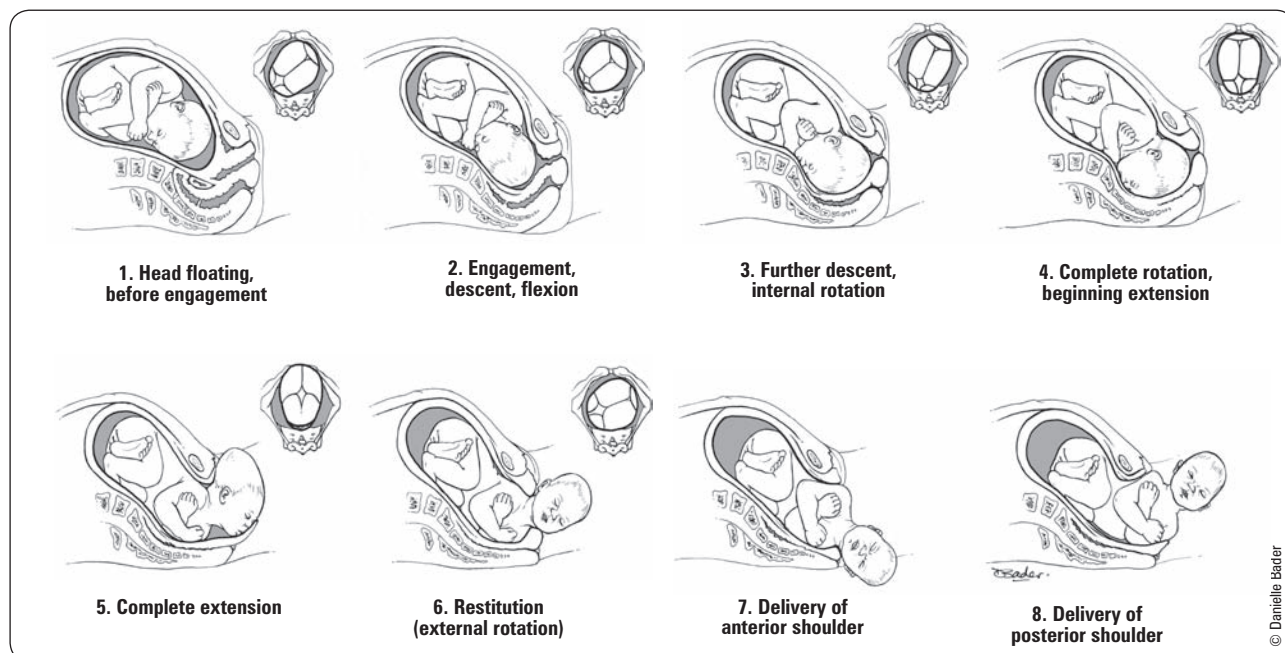
**Outcome:** Effects on mothers and their babies.

**Results:** Continuous intrapartum support increased likelihood of shorter labour, spontaneous vaginal birth, decrease in analgesia use, and a decrease in dissatisfaction with childbirth experience. Greatest benefit when provider is not a health care professional. Continuous support was also associated with decreased likelihood to have a Caesarian or instrumental vaginal birth, regional analgesia, or a baby with a low 5 min APGAR score.

### Fourth Stage of Labour

- first postpartum hour
- monitor vital signs and bleeding
- repair lacerations
- ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
- inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
- 3rd and 4th stages of labour most dangerous to the mother (i.e. hemorrhage)

## The Cardinal Movements of the Fetus During Delivery



**Figure 8. Cardinal movements of fetus during delivery**

Adapted from illustration in Williams Obstetrics, 19th ed

## Analgesic and Anesthetic Techniques in Labour and Birth

- pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

### Non-pharmacologic Pain Relief Techniques

- reduction of painful stimuli
  - maternal movement, position change, counter-pressure, abdominal compression
- activation of peripheral sensory receptors
  - superficial heat and cold
  - immersion in water during labour
  - touch and massage, acupuncture and acupressure
  - TENS
  - intradermal injection of sterile water
  - aromatherapy
- enhancement of descending inhibitory pathways
  - attention focusing and distraction
  - hypnosis
  - music and audio analgesia
  - biofeedback

### Pharmacologic Methods (see [Anesthesia](#), A22)

- nitrous oxide (e.g. self-administered Entonox®)
- narcotics (usually combined with anti-emetic)
- pudendal nerve block
- perineal infiltration with local anesthetic
- regional anesthesia (epidural block, CSE, spinal)



## Fetal Monitoring in Labour

- see online [Fetal Heart Rate Tutorial](#)

### Vaginal Exam

- membrane status
- cervical effacement (thinning), dilatation, consistency, position, application
- fetal presenting part, position, station
- bony pelvis size and shape
- monitor progress of labour at regular intervals and document in a partogram

### Intrapartum Fetal Monitoring

- intermittent fetal auscultation with Doppler device q15-30min for 1 min in first stage active phase following a contraction, q5min during second stage when pushing has begun
- continuous electronic FHR monitoring reserved for abnormal auscultation, prolonged labour, and labour which is induced or augmented
  - routine use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate
  - techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
- fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (CTG) to resolve the interpretation of abnormal or atypical patterns

### Electronic FHR Monitoring

- FHR measured by Doppler; contractions measured by tocometer
- described in terms of baseline FHR, variability (short term, long term) and periodicity (accelerations, decelerations)
- **Baseline FHR**
  - normal range is 110-160 bpm
  - parameter of fetal well-being vs. distress
- **Variability**
  - physiologic variability is a normal characteristic of FHR
  - variability is measured over a 15 min period and is described as: absent, minimal (less than 6 bpm), moderate (6-25 bpm), marked (greater than 25 bpm)
  - normal variability indicates fetal acid-base status is acceptable
  - can only be assessed by electronic fetal monitoring (CTG)
  - variability decreases intermittently even in healthy fetus (see Table 21)
- **Periodicity**
  - accelerations: increase of  $\geq 15$  bpm lasting  $\geq 15$  s, in response to fetal movement or uterine contraction (or  $\geq 10$  bpm lasting  $\geq 10$  s if  $< 32$  wk GA)
  - decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability (see Table 20)

**Table 19. Factors Affecting Fetal Heart Rate**

	<b>Fetal Tachycardia (FHR &gt; 160)</b>	<b>Fetal Bradycardia (FHR &lt; 110)</b>	<b>Decreased Variability</b>
<b>Maternal Factors</b>	Fever Hyperthyroidism Anemia	Hypothermia Hypotension Hypoglycemia	Infection Dehydration
<b>Fetal Factors</b>	Arrhythmia Anemia	Rapid descent Dysrhythmia Heart block	CNS anomalies Dysrhythmia Inactivity/sleep cycle, preterm fetus
<b>Drugs</b>	Sympathomimetics	$\beta$ -blockers Anesthetics	Narcotics, sedatives Magnesium sulphate, $\beta$ -blockers
<b>Uteroplacental</b>	Early hypoxia (abruption, HTN) Chorioamnionitis	Late hypoxia (abruption, HTN) Acute cord prolapse Hypercontractility	Hypoxia

### Fetal Scalp Blood Sampling

- indicated when atypical or abnormal fetal heart rate is suggested by clinical parameters including heavy meconium or moderately to severely abnormal FHR patterns, including unexplained low variability, repetitive late decelerations, complex variable decelerations, fetal cardiac arrhythmias
  - pH  $\geq 7.25$ : normal, repeat if abnormal FHR persists
  - pH 7.21-7.24: repeat assessment in 30 min or consider delivery if rapid fall since last sample
  - pH  $\leq 7.20$ : indicates fetal acidosis, delivery is indicated



#### Continuous CTG as a Form of EFM for Fetal Assessment during Labour

*Cochrane DB Syst Rev 2006;3:CD006066*

**Purpose:** To examine the effectiveness of continuous fetal heart monitoring (cardiotocography) during labour on improving health outcomes.

**Methods:** Systematic review comparing continuous fetal monitoring with no monitoring, intermittent auscultation, and intermittent monitoring.

**Results:** 12 trials (37,000 women) meeting search criteria were identified, of which 2 trials were high quality. Continuous electronic fetal heart monitoring did not have an effect on overall perinatal death rate compared to intermittent auscultation, with a relative risk (RR) of 0.85, 95% CI 0.59-1.23. Continuous monitoring also led to increased incidence of C/S (RR 1.66, 95% CI 1.30 to 2.13,  $n=18,761$ , 10 trials) and instrument assisted vaginal delivery (RR 1.16, 95% CI 1.01 to 1.32,  $n=18,151$ , nine trials). These results appeared consistent regardless if pregnancy was high risk, low risk, or preterm.

**Conclusion:** Continuous fetal cardiotocography does not significantly improve infant mortality or other standards of infant well-being. It increases the incidence of C/S and instrument assisted vaginal delivery.

- contraindications
  - known or suspected fetal blood dyscrasia (hemophilia, von Willebrand disease)
  - active maternal infection (HIV, genital herpes)

**Table 20. Comparison of Decelerations**

<b>Early Decelerations</b> <ul style="list-style-type: none"> <li>• Uniform shape with onset early in contraction, returns to baseline by end of contraction, mirrors contraction</li> <li>• Gradual deceleration</li> <li>• Often repetitive; no effect on baseline FHR or variability</li> <li>• Benign, due to vagal response to head compression</li> </ul>	
<b>Variable Decelerations</b> <ul style="list-style-type: none"> <li>• Variable in shape, onset, and duration</li> <li>• Most common type of periodicity seen during labour</li> <li>• Often with abrupt drop in FHR; usually no effect on baseline FHR or variability</li> <li>• Due to cord compression or, in second stage, forceful pushing with contractions</li> </ul>	
<b>Complicated Variable Decelerations</b> <ul style="list-style-type: none"> <li>• To &lt;70 bpm for &gt;60 s</li> <li>• Loss of variability or decrease in baseline after deceleration</li> <li>• Biphasic deceleration</li> <li>• Slow return to baseline</li> <li>• Baseline tachycardia or bradycardia</li> </ul>	
<b>Late Decelerations</b> <ul style="list-style-type: none"> <li>• Uniform shape with onset late in contraction, nadir after peak of contraction, and slow return to baseline</li> <li>• May cause decreased variability and change in baseline FHR</li> <li>• Due to fetal hypoxia and acidemia, maternal hypotension or uterine hypertonus</li> <li>• Usually a sign of uteroplacental insufficiency (an ominous sign)</li> </ul>	



**Rule of 60s Suggesting Severe Variable Decelerations:**  
 Deceleration to <60 bpm  
 >60 bpm below baseline  
 >60 s in duration with slow return to baseline

**Table 21. Classification of Intrapartum EFM Tracings**

	Normal Tracing (Category 1)	Atypical Tracing* (Category 2)	Abnormal Tracing* (Category 3)
<b>Baseline</b>	110-160 bpm	Bradycardia 100-110 bpm Tachycardia >160 for 30-80 min Rising baseline	Bradycardia <100 bpm Tachycardia >160 bpm for >80 min Erratic baseline
<b>Variability</b>	6-25 bpm ≤5 bpm for <40 min	≤5 bpm for 40-80 min	<5 bpm for >80 min ≥25 bpm for >10 min
<b>Decelerations</b>	None Early decelerations Occasional uncomplicated variable decelerations	Repetitive (≥3) uncomplicated variable decelerations Occasional late decelerations Any prolonged deceleration 2-3 min	Repetitive (≥3) complicated variable decelerations Repetitive late decelerations Any prolonged deceleration >3 min
<b>Accelerations</b>	Accelerations spontaneous or during scalp stimulation	Absent with scalp stimulation	Nearly absent
<b>Action</b>	EFM may be interrupted for ≤30 min if mother/fetus stable	Further assessment required	Action required: review clinical situation, obtain scalp pH, prepare for possible delivery

Adapted from SOGC guidelines, September 2008

\*Previous classification was "reassuring" vs. "non-reassuring", but distinction is now made between tracings that have some concerning changes but do not require immediate action (atypical) versus those with major concerns requiring immediate intervention (abnormal)



#### Approach to the Management of Abnormal FHR

**POISON – ER**  
 Position (LLPD)  
 O<sub>2</sub> (100% by mask)  
 IV fluids (corrects maternal hypotension)  
 Fetal Scalp stimulation  
 Fetal Scalp electrode  
 Fetal Scalp pH  
 Stop Oxygen  
 Notify MD

Vaginal Exam to r/o cord prolapse  
 Rule out fever, dehydration, drug effects, prematurity

- If above fails, consider C/S

### Fetal Oxygenation

- uterine contractions during labour decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow and have no adverse effects
- distribution of oxygen to the fetus depends on maternal, uteroplacental and fetal factors



- **fetal response to hypoxia/asphyxia**
  - decreased movement, tone, and breathing activities
  - redistribution of fetal blood flow
    - ♦ increased flow to brain, heart, and adrenals
    - ♦ decreased flow to kidneys, lungs, gut, liver and peripheral tissues
    - ♦ increase in blood pressure
  - transient fetal bradycardia followed by fetal tachycardia
  - anaerobic metabolism (decreased pH)

**Table 22. Factors Affecting Fetal Oxygenation**

Factor	Mechanism	Example
<b>Maternal</b>	Decreased maternal oxygen carrying capacity	Significant anemia (iron deficiency, hemoglobinopathies), carboxyhemoglobin (smokers)
	Decreased uterine blood flow	Hypotension (blood loss, sepsis), regional anesthesia, maternal positioning
	Chronic maternal conditions	Vasculopathies (SLE, Type 1 DM, chronic HTN), antiphospholipid syndrome, cyanotic heart disease, COPD
<b>Uteroplacental</b>	Uterine hypertonus	Placental abruption, hyperstimulation secondary to oxytocin, prostaglandins or normal labour
	Uteroplacental dysfunction	Placental abruption, placental infarction (dysfunction marked by IUGR, oligohydramnios, abnormal Doppler studies), chorioamnionitis, placental edema (diabetes, hydrops), placental senescence (post- dates)
<b>Fetal</b>	Cord compression	Oligohydramnios, cord prolapse or entanglement
	Decreased fetal oxygen carrying capacity	Significant anemia (isoimmunization, feto-maternal bleed), carboxyhemoglobin (exposure to smokers)

## Induction of Labour

### Definition

- artificial initiation of labour before its spontaneous onset for the purpose of delivery of the fetus and placenta

### Prerequisites for Labour Induction

- capability for C/S if necessary
- maternal
  - short, thin, soft, anterior cervix with open os (“inducible” or “ripe”)
  - if cervix is not ripe, use prostaglandin vaginal insert (Cervidil®), prostaglandin gel (Prepidil®), or Foley catheter
- fetal
  - normal fetal heart tracing
  - cephalic presentation
  - adequate fetal monitoring available
- likelihood of success determined by Bishop score
  - cervix considered unfavourable if <6
  - cervix favourable if ≥6
  - score of 9-13 associated with high likelihood of vaginal delivery

**Table 23. Bishop Score**

Cervical characteristic	0	1	2	3
<b>Position</b>	Posterior	Mid	Anterior	–
<b>Consistency</b>	Firm	Medium	Soft	–
<b>Effacement (%)</b>	0-30	40-50	60-70	≥80
<b>Dilatation (cm)</b>	0	1-2	3-4	≥5
<b>Station of fetal head</b>	-3	-2	-1, 0	+1, +2, +3

### Indications

- post-dates pregnancy (generally >41 wk) = most common reason for induction
- maternal factors
  - diabetes mellitus = second most common reason for induction
  - gestational HTN
  - other maternal medical problems, e.g. renal or lung disease
- maternal-fetal factors
  - isoimmunization, PROM, chorioamnionitis, post-term pregnancy



#### Induction vs. Augmentation

**Induction** is the artificial initiation of labour.

**Augmentation** promotes contractions when spontaneous contractions are inadequate.



Induction is indicated when the risk of continuing pregnancy exceeds the risks associated with induced labour and delivery.



#### Consider the Following before Induction

- Indication for induction
- Contraindications
- GA
- Cervical favourability
- Fetal presentation
- Potential for CPD
- Fetal well-being/FHR
- Membrane status



- fetal factors
  - suspected fetal jeopardy as evidenced by biochemical or biophysical indications
  - fetal demise, IUGR

### Risks

- failure to achieve labour and/or vaginal birth
- uterine hyperstimulation and fetal compromise
- maternal side effects to medications
- uterine atony and PPH
- uterine rupture

### Contraindications

- maternal
  - prior classical or inverted T-incision or uterine surgery (e.g. myomectomy)
  - unstable maternal condition
  - active maternal genital herpes
  - invasive cervical carcinoma
  - pelvic structure deformities
- maternal-fetal
  - placenta previa or vasa previa
  - cord presentation
- fetal
  - fetal distress, malpresentation, preterm fetus without lung maturity



#### Evidence for Cervical Ripening Methods (SOGC Guidelines)

- Meta-analysis of five trials has concluded that the use of oxytocin to ripen the cervix is not effective
- Since the best dose and route of misoprostol for labour induction with a live fetus are not known and there are concerns regarding hyperstimulation, the use of misoprostol for induction of labour should be within clinical trials only (Level 1b evidence) or in cases of intrauterine fetal death to initiate labour



#### Intravaginal PGE2 (Cervidil®) Compared to Intravaginal Prostaglandin Gel

4 RCTs have compared the two with varying results, depending on the dosing regime of gel used.

Theoretical advantages of Cervidil®:

- Insertion without a speculum
- Slow, continuous release
- Only one dose required
- Ability to use oxytocin 30 min after removal
- Ability to remove insert if required (i.e. excessive uterine activity)

## Induction Methods

### CERVICAL RIPENING

#### Definition

- use of medications or other means to soften, efface and dilate the cervix to increase likelihood of induction success
- ripening of an unfavourable cervix (Bishop score <6) is warranted prior to induction of labour

#### Methods

- intravaginal prostaglandin PGE2 gel (Prostin® gel): long and closed cervix
  - recommended dosing interval of prostaglandin gel is every 6 to 12 h up to 3 doses
- intravaginal PGE2 (Cervidil®): long and closed cervix, may use if ROM
  - continuous release, can be removed if needed
  - controlled release PGE2
- Foley catheter placement to mechanically dilate the cervix

### INDUCTION OF LABOUR

#### Amniotomy

- artificial rupture of membranes (amniotomy) to stimulate PG synthesis and secretion; may try this as initial measure if cervix is dilated
- few studies address the value of amniotomy alone for induction of labour
- amniotomy plus intravenous oxytocin: more women delivered vaginally at 24 h than amniotomy alone (relative risk = 0.03) and had fewer instrumental vaginal deliveries (relative risk = 5.5)

#### Oxytocin

- oxytocin (Pitocin®): 10 U in 1L NS, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60 min to a max of 36-48 mU/min
  - reduces rate of unsuccessful vaginal deliveries within 24 h when used alone (8.3% vs. 54%, RR 0.16)
  - ideal dosing regime of oxytocin is not known
  - current recommendations: use the minimum dose to achieve active labour and increase q30min as needed
  - reassessment should occur once a dose of 20 mU/min is reached
- potential complications
  - hyperstimulation/tetanic contraction (may cause fetal distress or rupture of uterus)
  - uterine muscle fatigue, uterine atony (may result in PPH)
  - vasopressin-like action causing anti-diuresis

## Augmentation of Labour

- augmentation of labour is used to promote adequate contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur
- oxytocin (0.5-2 mU/min IV increasing by 1-2 mU/min q20-60 min to a max of 36-48 mU/min)



Oxytocin  $t_{1/2}$  = 3-5 min.

# High Risk Labour and Delivery



## Preterm Labour

### Definition

- labour occurring between 20 and 37 wk gestation

### Etiology

- idiopathic (most common)
- maternal: infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), genital infection (bacterial vaginosis is associated with a 2-fold increase in relative risk of preterm birth), HTN, DM, chronic illness, mechanical factors, previous obstetric, gynecological and abdominal surgeries, socio-environmental (poor nutrition, smoking, drugs, alcohol, stress)
- maternal-fetal: PPRM (common), polyhydramnios, placenta previa or abruption, placental insufficiency
- fetal: multiple gestation, congenital abnormalities of fetus, fetal hydrops
- uterine: incompetent cervix, excessive enlargement (hydramnios), malformations (leiomyomas, septate uterus)

### Epidemiology

- preterm labour complicates about 10% of pregnancies

### Risk Factors and Prediction of PTL

- maternal risk scoring using above etiologies fails to identify up to 70% of preterm deliveries and is therefore of limited use
- prior history of spontaneous PTL: most important risk factor
- prior history cervical excisions or mechanical dilatation
- cervical length: measured by transvaginal U/S (cervical length >30 mm has high negative predictive value for PTL before 34 wk)
- identification of bacterial vaginosis (Rx metronidazole) and ureaplasma urealyticum (Rx erythromycin) infections: routine screening not supported by current data but it is reasonable to screen high risk women
- fetal fibronectin: a glycoprotein in amniotic fluid and placental tissue functioning to maintain integrity of chorionic-decidual interface in asymptomatic women
  - positive if >50 ng/mL
  - in symptomatic women (i.e. preterm contractions), fetal fibronectin is most effectively combined with U/S detecting cervical length
  - if cervical length is not short and fetal fibronectin is negative, preterm labour is highly unlikely



Positive fetal fibronectin in cervicovaginal fluid (>50 ng/mL) at 24 wk gestation predicted spontaneous PTL at <34 wk with sensitivity of 23%, specificity of 97%, PPV of 25%, NPV of 96%.

### Clinical Features

- regular contractions (2 in 10 min)
- cervix >2 cm dilated or 80% effaced or documented change in cervix

### Management

#### A. Initial

- transfer to appropriate facility if stable
- hydration (NS at 150 mL/h)
- bed rest in LLDP
- sedation (morphine)
- avoid repeated pelvic exams (increased infection risk)
- U/S examination of fetus (GA, BPP, position, placenta location, estimated fetal weight)
- prophylactic antibiotics; controversial but may help delay delivery, important to consider if PPRM

#### B. Suppression of Labour – Tocolysis

- does not inhibit preterm labour completely, but may buy time to allow for betamethasone valerate (Celestone®) and/or transfer to appropriate centre
- requirements (all must be satisfied)
  - preterm labour
  - live, immature fetus, intact membranes, cervical dilatation of <4 cm
  - absence of maternal or fetal contraindications
- contraindications
  - maternal: bleeding (placenta previa or abruption), maternal disease (hypertension, diabetes, heart disease), preeclampsia or eclampsia, chorioamnionitis
  - fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)
- tocolytic procedure
  - should be used only for <48 h and/or until transfer to an appropriate facility for care of the premature infant

- agents
  - calcium channel blockers: Nifedipine
    - 20 mg PO loading dose followed by 20 mg PO 90 min later. 20 mg can be continued q3-8h for 72 h or to a max of 180 mg
    - 10 mg PO q20min x 4 doses
  - prostaglandin synthesis inhibitors: Indomethacin
    - 1st line for early preterm labour (<30 wk GA) or polyhydramnios
    - 50-100 mg PO loading dose followed by 25 mg q4-6h
    - Magnesium sulphate was previously used for tocolysis. Currently, its primary use in obstetrics is limited to neuroprotection.

### C. Enhancement of Fetal Pulmonary Maturity

- betamethasone valerate (Celestone\*) 12 mg IM q24h x 2 or dexamethasone 6 mg IM q12h x 4
  - 28-34 wk GA: reduces incidence of RDS
  - 24-28 wk GA: reduces severity of RDS, overall mortality and rate of IVH
  - specific maternal contraindications: active TB

### D. Cervical Cerclage

- definition: placement of cervical sutures at the level of the internal os, usually at the end of the first trimester and removed in the third trimester
- indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
  - emerging evidence indicates that progesterone suppositories are superior to cerclage in preventing preterm labour late in pregnancy
- diagnosis of cervical incompetence
  - obstetrical Hx: silent cervical dilation
  - ability of cervix to hold an inflated Foley catheter during a hysterosonogram
- proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. conization of the cervix, connective tissue disorders)
- benefit is variable in those with secondary cervical incompetence causing premature ripening of the cervix (e.g. infection, abnormal placentation)

### Prognosis

- prematurity is the leading cause of perinatal morbidity and mortality
- 30 wk or 1,500 g (3.3 lb) = 90% survival
- 33 wk or 2,000 g (4.4 lb) = 99% survival
- morbidity due to asphyxia, hypoxia, sepsis, RDS, intraventricular cerebral hemorrhage, thermal instability, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis

### Prevention of Preterm Labour

- currently there are no agents approved by Health Canada to arrest preterm labour
- preventative measures: good prenatal care, identify pregnancies at risk, treat silent vaginal infection or UTI, patient education
- transvaginal ultrasound of cervical length is recommended only for high-risk pregnancies



#### Cerclage for Short Cervix on Ultrasonography in Women With Singleton Gestations and Previous Preterm Birth

*Obstet Gynecol* 2011;117:663-671

**Purpose:** To determine if cerclage prevents preterm birth (<35 wk gestation) and perinatal mortality and morbidity among women with previous spontaneous preterm birth, asymptomatic singleton gestation, and short cervical length (<25 mm before 24 wk gestation) on transvaginal ultrasonography.

**Methods:** Meta-analysis of randomized trials identified using searches on MEDLINE, PUBMED, EMBASE and the Cochrane Library.

**Results:** 5 trials included. Preterm birth was significantly lower among women receiving cerclage versus those not (RR = 0.70, 95% CI: 0.55, 0.89). Cerclage also significantly reduced preterm birth before 24, 28, 32, and 37 wk of gestation. Perinatal mortality and morbidity were significantly lower in the cerclage group (RR = 0.64, 95% CI: 0.45, 0.91).

**Conclusions:** Cerclage significantly prevents preterm birth and perinatal mortality and morbidity in this specific group of women.



#### Membrane Status Determined by

- Pooling of fluid on speculum exam
- Increase pH of vaginal fluid (nitrazine test)
- Ferning of fluid under light microscopy
- Decreased AFV on U/S



#### L/S Ratio (Lecithin:Spingomyelin Ratio)

Lecithin levels increase rapidly after 35 wk gestation, whereas sphingomyelin levels remain relatively constant. The L/S ratio is a measure of fetal lung maturity – less than 2:1 indicates pulmonary immaturity. Presence of blood or meconium in the amniotic fluid can affect the ratio.

## Premature Rupture of Membranes

### Definitions

- PROM or amniorrhexis: rupture of membranes prior to labour at any GA
- prolonged ROM: >24 h elapsed between rupture of membranes and onset of labour
- preterm ROM: ROM occurring before 37 wk gestation (associated with PTL)
- PPROM: rupture of membranes before 37 wk AND prior to onset of labour

### Risk Factors

- maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STI, UTI), family history of PROM, low socioeconomic class/poor nutrition
- fetal: congenital anomaly, multiple gestation
- other risk factors associated with PTL

### Clinical Features

- history of fluid gush or continued leakage

### Investigations

- sterile speculum exam (avoid introduction of infection)
  - pooling of fluid in the posterior fornix
  - may observe fluid leaking out of cervix on cough/Valsalva (“cascade”)
- nitrazine (amniotic fluid turns nitrazine paper blue)
  - low specificity as can be positive with blood, urine or semen
- ferning (high salt in amniotic fluid evaporates, looks like ferns under microscope)
- U/S to r/o fetal anomalies, assess GA and BPP

## Management

- admit for expectant management and monitor vitals q4h, daily BPP and WBC count
- avoid introducing infection with examinations (do NOT do a bimanual exam)
- cultures (cervix for GC, lower vagina for GBS)
- assess fetal lung maturity by L/S ratio of amniotic fluid
  - consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <32 wk and no evidence of infection
  - consider tocolysis for 48 h to permit administration of steroids if PPROM induces labour
- if not in labour or labour not indicated, consider antibiotics (controversial)
  - studies show broad spectrum coverage increases the time to onset of labour from PROM by 5-7 d with no increase in maternal or neonatal morbidity or mortality
- deliver urgently if evidence of fetal distress and/or chorioamnionitis

**Table 24. PROM Management**

Degree of Prematurity	Management
<24 wk	Consider termination (poor outcome due to pulmonary hypoplasia)
24-25 wk	Individual consideration with counselling of parents re: risks to preterm infants
26-34 wk	Expectant management as prematurity complications are significant
34-36 wk	"Grey zone" where risk of death from RDS and neonatal sepsis is the same
≥37 wk	Induction of labour since the risk of death from sepsis is greater than RDS

## Prognosis

- varies with gestational age
- 90% of women with PROM at 28-34 wk GA go into spontaneous labour within 1 wk
- 50% of women with PROM at <26 wk GA go into spontaneous labour within 1 wk
- complications: cord prolapse, intrauterine infection (chorioamnionitis), premature delivery, limb contracture

## Breech Presentation

### Definition

- fetal buttocks or lower extremity is the presenting part as determined on U/S (see Figure 9)
- complete (10%): flexion at hips and knees
- frank (60%): flexion at hips, extension at knees
- most common type of breech presentation
- most common breech presentation to be delivered vaginally
- footling (30%): may be single or double with extension at hip(s) and knee(s) so that foot is the presenting part

### Epidemiology

- occurs in 3-4% of pregnancies at term (25% before 28 wk)

### Risk Factors

- maternal: pelvis (contracted), uterus (shape abnormalities, intrauterine tumours, fibroids), extrauterine tumours causing compression, grand multiparity
- maternal-fetal: placenta (previa), amniotic fluid (poly/oligohydramnios)
- fetal: prematurity, multiple gestation, congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations), abnormalities in fetal tone and movement, aneuploidy

### Management

- ECV: repositioning of fetus within uterus under U/S guidance
  - overall success rate of 65%
  - criteria: <37 wk, singleton, unengaged presenting part, reactive NST
  - contraindications: previous T3 bleed, prior classical C/S, previous myomectomy, oligohydramnios, PROM, placenta previa, abnormal U/S, suspected IUGR, hypertension, uteroplacental insufficiency, nuchal cord
  - risks: abruption, cord compression
  - method: tocometry, followed by ultrasound guided transabdominal manipulation of fetus with consistent fetal heart monitoring
  - if patient Rh negative, give Rhogam® prior to procedure
  - good prognostic factors (for a successful version)
    - ♦ multiparous, good fluid volume, small baby, skilled obstetrician
- pre- or early labour ultrasound to assess type of breech presentation, fetal growth, estimated weight, attitude of fetal head; if ultrasound unavailable, recommend C/S
- trial of labour and elective C/S should be presented as options with the risks and benefits outlined; obtain informed consent



**A. Complete Breech**



**B. Frank Breech**



**C. Footling Breech**

© Crista Mason 2004

**Figure 9. Types of breech presentation**



#### Criteria for Vaginal Breech Delivery

- Frank or complete breech, GA >36 wk
- EFW 2,500-3,800 g based on clinical and U/S assessment (5.5-8.5 lb)
- Fetal head flexed
- Continuous fetal monitoring
- 2 experienced obstetricians, assistant, and anesthetist present
- Ability to perform emergency C/S within 30 min if required

- method for vaginal breech delivery:
  - encourage effective maternal pushing efforts
  - at delivery of after-coming head, assistant must apply suprapubic pressure to flex and engage fetal head
  - delivery can be spontaneous or assisted; avoid fetal traction
  - apply fetal manipulation only after spontaneous delivery to level of umbilicus
- C/S recommended if: the breech has not descended to the perineum in the second stage of labour after 2 h, in the absence of active pushing, or if vaginal delivery is not imminent after 1 h of active pushing
- contraindications to vaginal breech delivery:
  - cord presentation
  - clinically inadequate maternal pelvis
  - fetal factors incompatible with vaginal delivery (see OB37)

### Prognosis

- regardless of route of delivery, breech infants have lower birth weights and higher rates of perinatal mortality, congenital anomalies, abruption and cord prolapse

## Vaginal Birth After Cesarean (VBAC) aka Trial of Labour After Cesarean (TOLAC)

- recommended after previous low transverse incision
- success rate varies with indication for previous C/S (generally 60-80%)
- risk of uterine rupture (<1% with low transverse incision)

### Contraindications

- previous classical, inverted T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
- history of hysterotomy or previous uterine rupture
- multiple gestation
- non-vertex presentation or placenta previa
- inadequate facilities or personnel for emergency C/S

## Prolonged Pregnancy

### Definition

- pregnancy beyond 42 wk GA

### Epidemiology

- 41 wk GA: up to 27%
- 42 wk GA: 4-14%

### Etiology

- most cases idiopathic
- anencephalic fetus with no pituitary gland
- placental sulfatase deficiency (X-linked recessive condition in 1/2,000-1/6,000 infants) – rare

### Clinical Features

- postmaturity syndrome: 10-20% of post-term pregnancies (fetal weight loss, reduction in subcutaneous fat, scaling, dry skin from placental insufficiency, long thin body, open-eyed, alert and worried look, long nails, palms and soles wrinkled)
- with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental aging and infarction, macrosomia, dystocia, fetal distress, operative deliveries

### Management

- GA 40-41 wk: expectant management
  - no evidence to support IOL or C/S unless other risk factors for morbidity are present (see prognosis)
- GA >41 wk: offer IOL if vaginal delivery is not contraindicated
  - IOL shown to decrease C/S, fetal heart rate changes, meconium staining, macrosomia and death when compared with expectant management
- GA >41 wk and expectant management elected: serial fetal surveillance
  - fetal movement count by the mother
  - BPP q3-4d
  - If AFI is decreased, labour will be induced



#### Vaginal Delivery of Breech Presentation

SOGG Clinical Practice Guideline, JOGC, 2009

**Objective:** To discuss risks and benefits of trial of labour versus planned C/S, with selection criteria, management and delivery techniques for trial of vaginal breech birth.

**Evidence:** Randomized trials, prospective cohort studies and select cohort studies from Medline search for long-term outcomes and epidemiology of vaginal breech delivery.

**Summary:** Higher risk of perinatal mortality and short-term neonatal morbidity can be associated with vaginal breech birth as compared to elective C/S. However, careful case selection (including term singleton breech fetuses and clinically adequate maternal pelvis) and labour management may achieve a similar safety level as elective C/S (approx. 2 per 1000 births perinatal mortality, approx. 2% short-term neonatal morbidity). Specific protocols for vaginal breech delivery should be followed: continuous fetal heart monitoring, assessment for adequate progress in labour, no induction of labour recommended, emergency C/S available if required and health care providers with requisite skills and experience. Informed consent for the preferred delivery method should be obtained.



#### VBAC

- Rate of VBAC ranges from 60-82%
- No significant difference in maternal deaths or hysterectomies between VBAC or C/S
- Uterine rupture more common in VBAC group
- Evidence regarding fetal outcome is lacking

Safety of vaginal birth after Cesarean section: A systematic review. *Obstet Gynecol* 2004;103:420-9



**Prognosis**

- if >41 wk, perinatal mortality 2-3x higher (due to progressive uteroplacental insufficiency)
- morbidity increased with hypertension in pregnancy, DM, abruption, IUGR and multiple gestation

## Intrauterine Fetal Death

**Definition**

- fetal death in utero after 20 wk GA

**Epidemiology**

- 1% of pregnancies

**Etiology**

- 50% idiopathic
- 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, APS

**Clinical Features**

- decreased perception of fetal movement by mother
- SFH and maternal weight not increasing
- absent fetal heart tones (not diagnostic)
- high MSAFP

**Management**

- diagnosis: absent cardiac activity and fetal movement on U/S required for diagnosis
- determine secondary cause
  - maternal: HbA1c, Kleihauer-Betke, VDRL, ANA, antibody screens, INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, TORCH screen
  - fetal: chromosomes, cord blood, skin biopsy, genetics evaluation, autopsy
  - placenta: pathology, bacterial cultures

**Treatment**

- induction of labour
- monitor for maternal coagulopathy (10% risk of DIC)
- parental psychological care as per hospital protocol
- comprehensive discussion within 3 mo about final investigation and post-mortem results, help make plans for future pregnancies

**DIC: Generalized Coagulation and Fibrinolysis Leading to Depletion of Coagulation Factors****Obstetrical Causes**

- Abruption
- Gestational HTN
- Fetal demise
- PPH

**DIC-specific Bloodwork**

- Platelets
- aPTT and PT
- FDP
- Fibrinogen

**Treatment**

- Treat underlying cause
- Supportive
  - Fluids
  - Blood products
    - FFP, platelets, cryoprecipitate
- Consider anti-coagulation as VTE prophylaxis

## Complications of Labour and Delivery



### Meconium in Amniotic Fluid

**Epidemiology**

- present early in labour in 10% of pregnancies
- in general, meconium may be present in up to 25% of all labours; usually NOT associated with poor outcome, but extra care is required at time of delivery to avoid aspiration

**Etiology**

- likely cord compression ± uterine hypertonus
- may indicate undiagnosed breech
- increasing meconium during labour may be a sign of fetal distress

**Features**

- consistency and colour:
  - light yellow/green or dark green-black in colour.
  - may be watery or thicker

**Treatment**

- call respiratory therapy, neonatology or pediatrics to delivery room
- oropharynx suctioning upon head expulsion or immediately after delivery if baby not breathing spontaneously (do NOT stimulate infant before)
- consider amnioinfusion of ~800 mL of IV NS over 50-80 min during active stage of labour and a maintenance dose of ~3 mL/min until delivery
- closely monitor FHR for signs of fetal distress



Dark green or black meconium is associated with lower APGARs and increased risk of meconium aspiration.



## Abnormal Progression of Labour (Dystocia)

### Definition

- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labour (see Figure 10)
- during active phase:  $>4$  h of  $<0.5$  cm/h
- during 2nd phase:  $>1$  h with no descent during active pushing

### Etiology

- Power (leading cause): contractions (hypotonic, incoordinate), inadequate maternal expulsive efforts
- Passenger: fetal position, attitude, size, anomalies (hydrocephalus)
- Passage: pelvic structure (CPD), maternal soft tissue factors (tumours, full bladder or rectum, vaginal septum)
- Psyche: hormones released in response to stress may contribute to dystocia. Psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed



Provided there are no contraindications, oxytocin is utilized to improve uterine contraction strength and/or frequency.



#### The 4 Ps of Dystocia

**P**ower  
**P**assenger  
**P**assage  
**P**syche

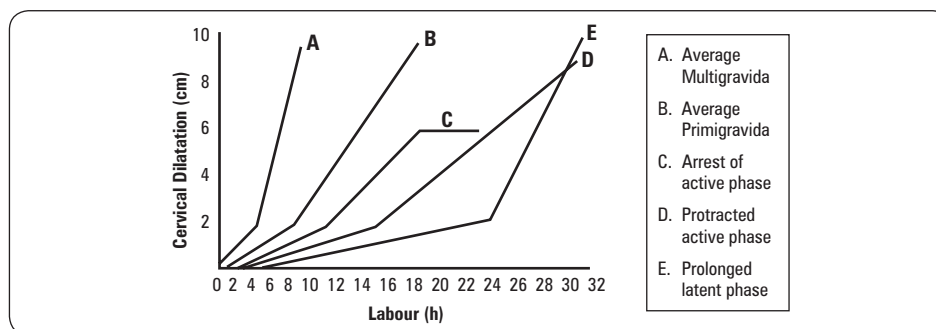


Figure 10. Normal and abnormal courses of the first stage of labour

### Arrest Disorder (Curve C)

- arrest of dilatation
  - dilatation progress does not occur for  $\geq 2$  h in a patient who has entered the active phase
  - arrest usually occurs at a cervical dilatation of 5-8 cm
- arrest of descent
  - no progress in station for  $>1$  h during second stage
  - should search for factors causing CPD (nearly 50% require C/S)
  - CPD diagnosed if adequate contractions measured by intrauterine pressure catheter (IUPC) with no descent/dilatation for  $>2$  h
  - if CPD ruled out, IV oxytocin and amniotomy can be attempted

### Protraction Disorders (Curve D)

- protraction of dilatation: slope of cervical dilatation  $<1.2$  cm/h in primigravidas or  $<1.5$  cm/h in multigravidas
- protraction of descent: a rate of descent of  $<1.0$  cm/h in primigravidas or  $2.0$  cm/h in multigravidas
- treatment: oxytocin augmentation if contractions are inadequate  $\pm$  amniotomy

### Prolonged Latent Phase (Curve E)

- $\geq 20$  h in primigravidas or  $\geq 14$  h in multigravidas during which labour has not progressed to the active phase
- most often due to false labour (avoid amniotomy for fear of false labour and increased risk of intrauterine infection)
- premature or excessive use of sedation or analgesia may play a role
- careful search for factors of CPD should be made
- management: oxytocin augmentation if diagnosis of labour is certain, otherwise rest  $\pm$  sedation

### Risks of Dystocia

- inadequate progression of labour is associated with an increased incidence of:
  - maternal stress
  - maternal infection
  - postpartum hemorrhage
  - need for neonatal resuscitation



Gynaecoid  
(50% obstetrically ideal)



Android (20%)



Anthropoid (25%)



Platypelloid (5%)

© Bonnie Tang 2012

Figure 11. Types of pelvis



- 1/3 of protraction disorders develop into 2<sup>nd</sup> arrest of dilatation due to CPD
- 2/3 of protraction disorders progress through labour to vaginal delivery

## Shoulder Dystocia

### Definition

- impaction of anterior shoulder of fetus against symphysis pubis after fetal head has been delivered
- life threatening emergency

### Etiology/Epidemiology

- incidence 0.15-1.4% of deliveries
- occurs when breadth of shoulders is greater than biparietal diameter of the head

### Risk Factors

- maternal: obesity, diabetes, multiparity
- fetal: prolonged gestation, macrosomia
- labour
  - prolonged 2nd stage
  - prolonged deceleration phase (8-10 cm)
  - instrumental midpelvic delivery

### Clinical Features

- “turtle sign”: head delivered but retracts against inferior portion of pubic symphysis
- complications
  - chest compression by vagina or cord compression by pelvis can lead to hypoxia
  - brachial plexus injury (Erb's palsy: C5-C7; Klumpke's palsy: C8-T1)
    - ♦ 90% resolve within 6 mo
  - fetal fracture (clavicle, humerus, cervical spine)
  - maternal perineal injury, may result in PPH

### Treatment

- goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved (see sidebar)
- other options:
  - cleidotomy (deliberate fracture of neonatal clavicle)
  - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent C/S
  - symphysiotomy

### Prognosis

- 1% risk of long term disability for infant



#### Approach to the Management of Shoulder Dystocia

##### ALARMER

Apply suprapubic pressure and ask for help

Legs in full flexion (McRobert's maneuver)

Anterior shoulder disimpaction (suprapubic pressure)

Release posterior shoulder by rotating it anteriorly with hand in the vagina under adequate anesthesia

Manual corkscrew i.e. rotate the fetus by the posterior shoulder until the anterior shoulder emerges from behind the maternal symphysis

Episiotomy

Rollover (on hands and knees)

\*Note that suprapubic pressure and McRoberts maneuver together will resolve 90% of cases

## Umbilical Cord Prolapse

### Definition

- descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

### Etiology/Epidemiology

- increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, CPD
- incidence: 0.17-0.63%

### Clinical Features

- visible or palpable cord
- FHR changes (variable decelerations, bradycardia or both)

### Treatment

- emergency C/S
- O<sub>2</sub> to mother, monitor fetal heart
- alleviate pressure of the presenting part on the cord by placing digit in vagina (maintain this position until C/S)
- keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
- position mother in Trendelenburg or knee-to-chest position
- if fetal demise or too premature (<22 wk), allow labour and delivery



#### Umbilical Cord Accident Causes

- Nuchal cord
  - Type A (looped)
  - Type B (hitched)
- Body loop
- Single artery
- True knot
- Torsion
- Velamentous
- Short cord <35 cm
- Long cord >80 cm

## Uterine Rupture



### Etiology/Epidemiology

- associated with previous uterine scar (in 40% of cases), hyperstimulation with oxytocin, grand multiparity and previous intrauterine manipulation
- generally occurs during labour, but can occur earlier with a classical incision
- 0.5-0.8% incidence, up to 12% with classical incision

### Clinical Features

- prolonged fetal bradycardia – most common presentation
- acute onset abdominal pain
- hyper or hypotonic uterine contractions
- vaginal bleed

### Risk Factors:

- uterine scarring (i.e. previous uterine surgeries including Cesarean, perforation with D&C)
- excessive uterine stimulation (i.e. protracted labour, oxytocin)
- uterine trauma (i.e. operative equipment, ECV)
- multiparity
- uterine abnormalities

### Treatment

- rule out placental abruption
- immediate delivery for fetal survival
- maternal stabilization (may require hysterectomy)

### Complications

- maternal mortality 1-10%
- maternal hemorrhage, shock, DIC
- amniotic fluid embolus
- hysterectomy if uncontrollable hemorrhage
- fetal distress, associated with 50% fetal mortality



#### Maternal Mortality Causes

- Thromboembolism
- Cardiac event
- Suicide
- Sepsis
- Ectopic pregnancy
- Hypertension
- Amniotic-fluid embolism
- Hemorrhage

\* In Canada (2005), lifetime risk of maternal death is 1 in 11,000

## Amniotic Fluid Embolus

### Definition

- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

### Etiology/Epidemiology

- rare intrapartum or immediate postpartum complication
- 60-80% maternal mortality rate, accounts for 10% of all maternal deaths
- leading cause of maternal death in induced abortions and miscarriages
- 1/8,000-1/80,000 births

### Risk Factors

- placental abruption
- rapid labour
- multiparity
- uterine rupture
- uterine manipulation

### Differential Diagnosis

- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruption, chronic coagulopathy

### Clinical Features

- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia) and coagulopathy
- seizure in 10%
- ARDS and left ventricular dysfunction seen in survivors

### Management

- supportive measures (high flow O<sub>2</sub>, ventilation support, fluid resuscitation, inotropic support, ± intubation), coagulopathy correction
- ICU admission

## Chorioamnionitis

### Definition

- infection of the chorion, amnion and amniotic fluid typically due to ascending infection by organisms of normal vaginal flora

### Etiology/Epidemiology

- incidence 1-5% of term pregnancies and up to 25% in preterm deliveries
- ascending from vagina
- predominant microorganisms include GBS, Bacteroides and *Prevotella* species, *E. coli* and anaerobic *Streptococcus*

### Risk Factors

- prolonged ROM, long labour, multiple vaginal exams during labour, internal monitoring
- bacterial vaginosis and other vaginal infections

### Clinical Features

- maternal fever, maternal or fetal tachycardia, uterine tenderness, foul and purulent cervical discharge

### Investigations

- CBC: leukocytosis
- amniotic fluid: leukocytes or bacteria

### Treatment

- IV antibiotics
  - ampicillin (2 g IV q6h) and gentamicin (1.5 mg/kg q8h)
  - anaerobic coverage i.e. clindamycin if C/S
- expedient delivery regardless of gestational age

### Complications

- bacteremia of mother or fetus, wound infection if C/S, pelvic abscess, infant meningitis



#### Clinical Features of Chorioamnionitis

- Temperature
- Tachycardia (maternal or fetal)
- Tenderness (uterine)
- Foul discharge



#### Prerequisites for Operative Vaginal Delivery

##### ABCDEFGHIJK

Anesthesia (adequate)

Bladder empty

Cervix fully dilated and effaced with ROM

Determine position of fetal head

Equipment ready (including facilities for emergent C/S)

Fontanelle (posterior fontanelle midway between thighs)

Gentle traction

Handle elevated

Incision (episiotomy)

once Jaw visible remove forceps

Knowledgeable operator

## Operative Obstetrics

### Operative Vaginal Delivery

#### Definition

- forceps or vacuum extraction

#### Indications

- fetal
  - atypical or abnormal fetal heart rate tracing
  - consider if second stage is prolonged as this may be due to poor contractions or failure of fetal head to rotate
- maternal
  - need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
  - exhaustion, lack of cooperation and excessive analgesia may impair pushing effort

### Forceps

#### Outlet Forceps Position

- head visible between labia in between contractions
- sagittal suture in or close to AP diameter
- rotation cannot exceed 45°

#### Low Forceps Position

- presenting part at station +2 or greater
- subdivided based on whether rotation less than or greater than 45 degrees

#### Mid Forceps Position

- presenting part below spines but above station +2
- rarely done

#### Types of Forceps

- Simpson forceps for OA presentations
- Kielland (rotational) forceps when rotation of head to OA is recessing
- Piper forceps for breech

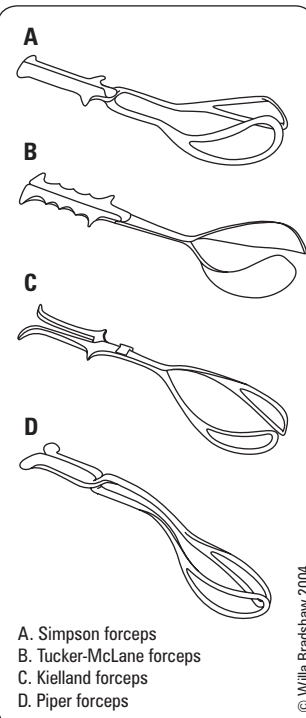


Figure 12. Types of forceps

## Vacuum Extraction

- traction instrument used as alternative to forceps delivery; aids maternal pushing

**Table 25. Advantages and Disadvantages of Forceps versus Vacuum Extraction**

	Forceps	Vacuum Extraction
<b>Advantages</b>	Higher overall success rate for vaginal delivery Decreased incidence of fetal morbidity	Easier to apply Less anesthesia required Less maternal soft-tissue injury compared to forceps
<b>Disadvantages</b>	Greater incidence of maternal injury	Contraindicated if fetus at risk for coagulation defect Suitable only for vertex presentations Maternal pushing required Contraindicated in preterm delivery
<b>Complications</b>	Maternal: anesthesia risk, lacerations, injury to bladder, uterus or bone, pelvic nerve damage, PPH, infections Fetal: fractures, facial nerve palsy, trauma to face/scalp, intracerebral hemorrhage, cephalohematoma, cord compression	Increased incidence of cephalohematoma and retinal hemorrhages compared to forceps Subglial hemorrhage, subaponeurotic hemorrhage, soft tissue trauma



### Limits for Trial of Vacuum

- After 3 pulls over 3 contractions with no progress, after 3 pop-offs with no obvious cause
- 20 min and delivery is not imminent



### Muscles of Perineal Body

- Superficial transverse perineal
- Bulbocavernosus
- External anal sphincter

## Lacerations

- first degree: involves skin and vaginal mucosa but not underlying fascia and muscle
- second degree: involves fascia and muscles of the perineal body but not the anal sphincter
- third degree: involves the anal sphincter but does not extend through it
- fourth degree: extends through the anal sphincter into the rectal mucosa

## Episiotomy

### Definition

- incision in the perineal body at the time of delivery
- essentially a controlled second degree laceration
- midline: incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernosus muscle
  - better healing but increased risk of deep tear
- mediolateral: incision through bulbocavernosus, superficial transverse perineal muscle, and levator ani
  - reduced risk of extensive tear but poorer healing and more pain
  - easier to repair

### Indications

- to relieve obstruction of the unyielding perineum
- instrumental delivery
- controversial between practitioners as to whether it is preferable to make a cut or let the perineum tear as needed
- current evidence suggests letting perineum tear and then repair as needed (restricted use)

### Complications

- infection, hematoma, extension into anal musculature or rectal mucosa, fistula formation, incontinence

## Cesarean Delivery

### Epidemiology

- incidence 20-25%

### Indications

- maternal: obstruction, active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery, underlying maternal illness (eclampsia, HELLP syndrome, heart disease)
- maternal-fetal: failure to progress, placental abruption or previa, vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, certain congenital anomalies



### Risk Factors for Primary and Subsequent Anal Sphincter Lacerations

*Am J Obstet Gynecol* 2007;196:344

**Objective:** Assess effects of pregnancy, delivery method and parity on risk of primary and secondary anal sphincter laceration in women with 1st vaginal delivery (VD), VBAC or 2nd VD.

**Methods:** Retrospective cohort study of all deliveries at one hospital from 1995-2002.

**Conclusion:** 20,674 live singleton deliveries were included. Women with first VD and VBAC both had OR 5.1 for laceration compared to 2nd VD. Factors that significantly increased risk of laceration for all 3 groups were: forceps and midline episiotomy. 2nd stage of labour >2 h only increased risk for 1st VD. Factors that had no significant increase in risk: infant birth weight >3,500 g, vacuum delivery. Women with prior anal sphincter laceration are at 3 times increased risk for subsequent sphincter laceration, compared with women with prior vaginal delivery without sphincter laceration.



### Restrictive vs. Routine Episiotomies with Vaginal Births

*Cochrane DB Syst Rev* 2009;1:CD000081

**Study:** This systematic review and meta-analysis of 8 RCTs assessed the effects of restrictive (only done for fetal indications or if severe perineal trauma was judged to be imminent) and routine (liberally done to prevent any tear) use of episiotomy during vaginal birth.

**Patients:** Of the 2709 patients in the routine episiotomy group, 2035 (75%) women had episiotomies. In the restrictive episiotomy group, 776 (28%) of the 2733 women had episiotomies.

**Results:** Restrictive episiotomies appear to have less severe perineal trauma (RR 0.67), less suturing (RR 0.71), and fewer healing complications at 7 d (RR 0.69) compared to routine episiotomies.

There is no difference for pain measures, dyspareunia, urinary incontinence, and severe vaginal or perineal trauma, but there was an increased risk of anterior perineal trauma (RR 1.84) with restrictive episiotomy. Similar results were obtained when comparing restrictive versus routine mediolateral versus midline episiotomy.

**Conclusions:** Compared to routine use, restrictive use of episiotomy during vaginal delivery appears to be more beneficial.

## Types of Cesarean Incisions

- skin
  - transverse (aka Pfannenstiel)
    - ♦ decreased exposure and slower entry
    - ♦ improved strength and cosmesis
  - vertical midline
    - ♦ rapid peritoneal entry and increased exposure
    - ♦ increased dehiscence
- uterine
  - low transverse (most common): in noncontractile segment
    - ♦ decreased chance for rupture in subsequent pregnancies
  - low vertical
    - ♦ used for very preterm infants, poorly developed maternal lower uterine segment
  - classical (rare): in thick, contractile segment
    - ♦ used for transverse lie, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid

## Risks/Complications

- anesthesia
- hemorrhage (average blood loss ~1,000 cc)
- infection (UTI, wound, endometritis)
- injury to surrounding structures (bowel, bladder, ureter, uterus)
  - single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g)
- thromboembolism
- increased recovery time/hospital stay
- maternal mortality (<0.1%)



### Common OR Questions

#### 7 layers to dissect

Skin, fatty layer, fascia, muscle separation (rectus abdominus), peritoneum, bladder flap, uterus

#### Layers of the rectus sheath

Above the arcuate line: external oblique, internal oblique, rectus abdominis, internal oblique, transversus abdominis  
Below the arcuate line: external oblique, internal oblique, transversus abdominis, rectus abdominis

**Name of the obliterated umbilical ligament**  
Urachus

# Puerperal Complications

- puerperium: 6 wk period of adjustment after pregnancy when pregnancy-induced anatomic and physiologic changes are reversed

## Postpartum Hemorrhage



### Definition

- loss of >500 mL of blood at the time of vaginal delivery, or >1,000 mL with C/S
- early – within first 24 h postpartum
- late – after 24 h but within first 6 wk

### Epidemiology

- incidence 5-15%

### Etiology (4 Ts)

#### 1. Tone

- uterine atony
  - ♦ most common cause of PPH
  - ♦ avoid by giving oxytocin with delivery of the anterior shoulder or placenta
  - ♦ occurs within first 24 h
- due to:
  - ♦ labour (prolonged, precipitous, induced, augmented)
  - ♦ uterus (infection, over-distention)
  - ♦ placenta (abruption, previa)
  - ♦ maternal factors (grand multiparity, gestational HTN)
  - ♦ halothane anesthesia

#### 2. Tissue

- retained placental products
- retained blood clots in an atonic uterus
- gestational trophoblastic neoplasia

#### 3. Trauma

- laceration (vagina, cervix, uterus), episiotomy, hematoma (vaginal, vulvar, retroperitoneal), uterine rupture, uterine inversion

#### 4. Thrombin

- coagulopathy
  - ♦ most identified prior to delivery (low platelets increases risk)
  - ♦ includes hemophilia, DIC, Aspirin® use, ITP, TTP, vWD (most common)
  - ♦ therapeutic anti-coagulation



Uterine atony is the most common cause of PPH.



### DDx of Early PPH – 4 Ts

Tone (atony)  
Tissue (retained placenta, clots)  
Trauma (laceration, inversion)  
Thrombin (coagulopathy)

### DDx of Late PPH

Retained products  
± endometritis  
Sub-involution of uterus



**Investigations**

- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of tone, tissue or trauma
- may be helpful to observe red-topped tube of blood – no clot in 7-10 min indicates coagulation problem

**Management**

- ABCs
- 2 large bore IVs and crystalloids
- CBC, coagulation profile, cross and type 4 units pRBCs
- treat underlying cause

**Medical Therapy**

- oxytocin 20 U/L NS or RL IV continuous infusion
  - in addition can give 10 U IMM after delivery of the placenta
- methylergonavine maleate (ergotamine) 0.25 mg IM/IMM q5min up to 1.25 mg; can be given as IV bolus of 0.125 mg (may exacerbate HTN)
- carboprost (Hemabate®), a synthetic PGF-1  $\alpha$  analog 0.25 mg IM/IMM q15min to max 2 mg (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary, renal and hepatic dysfunction)

**Local Control**

- bimanual compression: elevate the uterus and massage through patient's abdomen
- uterine packing (mesh with antibiotic treatment)
- Bakri Balloon for tamponade: may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR

**Surgical Therapy (Intractable PPH)**

- D&C (beware of vigorous scraping which can lead to Asherman's syndrome)
- embolization of uterine artery or internal iliac artery by interventional radiologist
- laparotomy with bilateral ligation of uterine artery (may be effective), internal iliac artery (not proven), ovarian artery, or hypogastric artery
- hysterectomy last option with angiographic embolization if post-hysterectomy bleeding

## Retained Placenta

**Definition**

- placenta undelivered after 30 min postpartum

**Etiology**

- placenta separated but not delivered
- abnormal placental implantation (placenta accreta, placenta increta, placenta percreta)

**Risk Factors**

- placenta previa, prior C/S, post-pregnancy curettage, prior manual placental removal, uterine infection

**Clinical Features**

- incomplete placenta removed
- risk of postpartum hemorrhage and infection

**Investigations**

- explore uterus
- assess degree of blood loss

**Management**

- 2 large bore IVs, type and screen
- Brant maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL NS into umbilical vein
- manual removal if above fails
- D&C if required

## Uterine Inversion



### Definition

- inversion of the uterus through cervix  $\pm$  vaginal introitus

### Etiology/Epidemiology

- often iatrogenic (excess cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous (lax uterine ligaments)
- 1/1500-1/2000 deliveries

### Clinical Features

- can cause profound vasovagal response with vasodilation and hypovolemic shock
- shock may be disproportionate to maternal blood loss

### Management

- urgent management essential, call anesthesia
- ABCs: initiate IV crystalloids
- can use tocolytic drug (see *Management of Preterm Labour*, OB38) or nitroglycerin IV to relax uterus and aid replacement
- replace uterus without removing placenta
- remove placenta manually and withdraw slowly
- IV oxytocin infusion (only after uterus replaced)
- re-explore uterus
- may require GA  $\pm$  laparotomy

## Postpartum Pyrexia

### Definition

- fever  $>38^{\circ}\text{C}$  on any 2 of the first 10 d postpartum, except the first day

### Etiology

- endometritis
- wound infection secondary to C/S
- mastitis/engorgement
- UTI
- atelectasis
- pneumonia

### Investigations

- detailed history and physical exam, relevant cultures
- for endometritis: blood and genital cultures

### Treatment

- depends on etiology
  - infection: empiric antibiotics, adjust when sensitivities available
    - ♦ endometritis: clindamycin + gentamycin IV
    - ♦ mastitis: cloxacillin or cefazolin
    - ♦ wound infection: cephalixin
  - DVT: anticoagulants
- prophylaxis against post-C/S endometritis: begin antibiotic immediately after cord clamping and administer only 1-3 doses – cefazolin is most common choice

### ENDOMETRITIS

- definition: infection of uterine myometrium and parametrium
- clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling discharge or lochia
- treatment: depends on infection severity; oral antibiotics if well, IV with hospitalization in moderate to severe cases

### VENOUS THROMBOEMBOLISM

- see *Venous Thromboembolism*, OB21



#### Etiology of Postpartum Pyrexia

##### B-5W

**Breast:** engorgement, mastitis

**Wind:** atelectasis, pneumonia

**Water:** UTI

**Wound:** episiotomy, C/S site infection

**Walking:** DVT, thrombophlebitis

**Womb:** endometritis



#### Risk Factors for Endometritis

C/S, intrapartum chorioamnionitis, prolonged labour, prolonged ROM, multiple vaginal examinations

## Mastitis



- definition: inflammation of mammary glands
- must r/o inflammatory carcinoma, as indicated
- differentiate from mammary duct ectasia: mammary duct(s) beneath nipple clogged and dilated ± ductal inflammation ± nipple discharge (thick, grey to green), often postmenopausal women

**Table 26. Lactational versus Non-Lactational Mastitis**

	Lactational	Non-Lactational
<b>Epidemiology</b>	More common than non-lactational Often 2-3 wk postpartum	Periductal mastitis most common Mean age 32 yr
<b>Etiology</b>	<i>S. aureus</i>	May be sterile May be infected with <i>S. aureus</i> or other anaerobes Smoking is risk factor May be associated with mammary duct ectasia
<b>Symptoms</b>	Unilateral localized pain Tenderness Erythema	Subareolar pain May have subareolar mass Discharge (variable colour) Nipple inversion
<b>Treatment</b>	Heat or ice packs Continued nursing/pumping Antibiotics (dicloxacillin/cephalexin) (Erythromycin if pen-allergic)	Broad-spectrum antibiotics and I&D Total duct excision (definitive)
<b>Abscess</b>	Fluctuant mass Purulent nipple discharge Fever, leukocytosis Discontinue nursing, IV antibiotics (nafcillin/oxacillin), I&D usually required	If mass does not resolve, FNA to exclude cancer and U/S to assess presence of abscess Treatment includes antibiotics, aspiration or I&D (tends to recur) May develop mammary duct fistula A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually <i>S. aureus</i> )

## Postpartum Mood Alterations

### POSTPARTUM BLUES

- 85% of new mothers, onset day 3-10; extension of the “normal” hormonal changes and adjustment to a new baby
- self-limited, should resolve by 2 wk
- manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness, fatigue, irritability, poor concentration/despondency

### POSTPARTUM DEPRESSION

- definition: major depression occurring in a woman within 6 mo of childbirth (see [Psychiatry](#), PS12)
- epidemiology: 10-20%, risk of recurrence 50%
- risk factors
  - personal or family history of depression (including PPD)
  - prenatal depression or anxiety
  - stressful life situation
  - poor support system
  - unwanted pregnancy
  - colicky or sick infant
- clinical features: suspect if the “blues” last beyond 2 wk, or if the symptoms in the first two wk are severe (e.g. extreme disinterest in the baby, suicidal or homicidal/infanticide ideation)
- assessment: Edinburgh Postnatal Depression Scale or other
- treatment: antidepressants, psychotherapy, supportive care, ECT if refractory
- prognosis: interferes with bonding and attachment between mother and baby so it can have long term effects



### POSTPARTUM PSYCHOSIS

- definition: onset of psychotic symptoms over 24-72 h within first month postpartum, can present in the context of depression
- epidemiology: rare (0.2%)

# Postpartum Care

## Postpartum Office Visit at 6 Weeks

### Care of Baby

- assess weight, feeding, immunization
- encourage breastfeeding if no contraindications

### Care of Mother (The 10 Bs)

- Be careful: do not use douches or tampons for 4-6 wk post-delivery
- Be fit: encourage gradual increases in walking, Kegel exercises
- Birth control: assess for use of contraceptives; breastfeeding is NOT an effective method of birth control (see [Gynecology](#), GY19 for more detail about different contraceptive options postpartum)
- Bladder: assess for urinary incontinence, maintain high fluid intake
- Bleeding: (see *Lacerations*, OB47), 300 µg of RhIG should be given if Rh+ fetus and Rh- mother or extensive bleeding at delivery
- Blood pressure: especially if gestational HTN
- Blood tests: glucose, CBC (for anemia as sign of hematomas, retained placenta)
- Blues: (see *Postpartum Mood Alterations*, OB51)
- Bowel: fluids and high-fibre foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain meds, doughnut cushion, Sitz baths, ice compresses
- Breast and pelvic exam: watch for Staphylococcal or Streptococcal mastitis/abscess, ± Pap smear at 6 wk

### Physiological Changes Postpartum

- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains firmness
  - should involute ~1 cm below umbilicus per day in first 4-5 d, reaches non-pregnant state in 4-6 wk postpartum
- ovulation resumes in ~45 d for non-lactating women and within 3-6 mo for lactating women
- lochia: normal vaginal discharge postpartum
  - decreases and changes in colour from red (lochia rubra; presence of erythrocytes) → yellow (lochia serosa) → white (lochia alba; residual leukorrhea) over 3-6 wk
  - foul smelling lochia suggests endometritis

### Breastfeeding Problems

- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisture cream, topical steroid if needed
- mastitis: treat promptly (see *Postpartum Pyrexia*, OB50)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see *Breastfeeding and Drugs*, OB53)

### Bladder Dysfunction

- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management: pelvic floor retraining with Kegel exercises, vaginal cones or pessaries, lifestyle modifications (e.g. limit fluid, caffeine intake)
- surgical management: minimally invasive procedures (tension-free vaginal tape, transobturator tape, midurethral sling) (see [Gynecology](#), GY35)

### Puerperal Pain

- “after pains” common in first 3 d due to uterine contractions; encourage simple analgesia
- ice packs can be used on perineum if painful
- encourage regular analgesia and stool softener



The acronym “**BUBBLES**” for what to ask about when rounding on postpartum care. Modify this for C/S or vaginal delivery

**B**aby care and breastfeeding (latch, amount)

**U**terus – firm or boggy?

**B**ladder function – Voiding well? Dysuria?

**B**owel function – Passing gas or stool? Constipated?

**L**ochia or discharge – Any blood?

**E**pisiotomy/laceration/incision – Pain controlled?

**S**ymptoms of VTE – Dyspnea? Calf pain?



## Breastfeeding and Drugs

**Table 27. Drug Safety During Breastfeeding**

Safe During Breastfeeding	Contraindicated to Breastfeeding
Analgesics (e.g. acetaminophen, NSAIDs)	Chloramphenicol (bone marrow suppression)
Anticoagulants (e.g. heparin)	Sulphonamides (in G6PD deficiency, can lead to hemolysis)
Antidepressants (e.g. sertraline, fluoxetine, TCAs)	Nitrofurantoin (in G6PD deficiency, can lead to hemolysis)
Antiepileptics (e.g. phenytoin, carbamazepine, valproic acid)	Tetracycline
Antihistamines	Lithium
Antimicrobials (e.g. penicillins, aminoglycosides, cephalosporins)	Anti-neoplastics and immunosuppressants
β-adrenergics (e.g. propranolol, labetalol)	Psychotropic drugs (relative contraindication)
Insulin	
Steroids	
OCP (low dose) – although may decrease breast milk production	



### Breastfeeding: Contraindicated Drugs

#### BREAST

Bromocriptine/Benzodiazepines  
Radioactive isotopes/Rizatriptan  
Ergotamine/Ethosuximide  
Amiodarone/Amphetamines  
Stimulant laxatives/Sex hormones  
Tetracycline/Tretinoin

## Common Medications

**Table 28. Common Medications**

Drug Name (Brand Name)	Dosing Schedule	Indications/Comments
betamethasone valerate (Celestone®)	12 mg IM q24h x 2 doses	Enhancement of fetal pulmonary maturity for PTL
carboprost (Hemabate®)	0.25 mg IM/IMM q15min; max 2 mg	Treatment of uterine atony
cefazolin	2 g IV then 1 g q8h	GBS prophylaxis (penicillin allergic and not at risk for anaphylaxis)
clindamycin	900 mg IVCV q8h	GBS prophylaxis (penicillin allergic and at risk for anaphylaxis)
dexamethasone	6 mg IM q12h x 4 doses	Enhancement of fetal pulmonary maturity for PTL
dinoprostone (Cervidil®: PGE <sub>2</sub> impregnated thread)	10 mg PV (remove after 12h) max of 3 doses	Induction of labour Advantage: can remove if uterine hyperstimulation
doxylamine succinate (Diclectin®)	2 tabs qhs + 1 tab qAM + 1 tab qPM max of 8 tabs/d	Each tablet contains 10 mg doxylamine succinate with vitamin B <sub>6</sub> Used for hyperemesis gravidarum
erythromycin	500 mg IV q6h	GBS prophylaxis (penicillin allergic and at risk for anaphylaxis)
folic acid	0.4-1 mg PO OD x 1-3 mo preconception and T1 5 mg PO OD with past Hx of NTD	Prevention of oNTD
methotrexate	50 mg/m <sup>2</sup> IM or 50 mg PO x 1 dose	For ectopic pregnancy or medical abortion
methylergonavine maleate (Ergotamine®)	0.25 mg IM/IMM q5min up to 1.25 mg or IV bolus 0.125 mg	Treatment of uterine atony
misoprostol (Cytotec®)	800-1000 µg PR x 1 dose 400 µg PO x 1 dose or 800 µg PV x 1 dose, 3 to 7 d after methotrexate	For treatment of PPH For medical abortion Also used for NSAID-induced ulcers (warn patients of contraindications)
oxytocin (Pitocin®)	0.5-2.0 mU/min IV, or 10 U/L NS incr. by 1-2 mU/min q20-60min max of 36-48 mU/min 10 U IM at delivery of anterior shoulder and of placenta 20 U/L NS or RL IV continuous infusion	Augmentation of labour (also induction of labour)  Prevention of uterine atony  Treatment of uterine atony
Penicillin G	5 million U IV then 2.5 million U IV q4h until delivery	GBS prophylaxis
PGE <sub>2</sub> gel (Prostin® gel)	0.5 mg PV q6-12h; max of 3 doses	Induction of labour
Rh IgG (Rhogam®)	300 µg IM x 1 dose	Given to Rh negative women • Routinely at 28 wk GA • Within 72 h of birth of Rh +ve fetus positive • Positive Kleihauer-Betke test • With any invasive procedure in pregnancy • Ectopic pregnancy • Antepartum hemorrhage • Miscarriage or TA (dose: 50 µg IM only)



### Common Discharge Medications

Oxycodone IR 5-10 mg PO q4-6h PRN  
Docusate sodium 100 mg PO bid



Misoprostol (Cytotec®) is also indicated to protect against NSAID-induced gastric ulcers in non-pregnant individuals. The use of misoprostol for cytoprotection is contraindicated in pregnancy. Warn female patients of this contraindication.

# References

- American College of Obstetricians and Gynecologists. Available from: [www.acog.org](http://www.acog.org).
- The Society of Obstetricians and Gynaecologists of Canada. Available from: [www.sogc.org](http://www.sogc.org).
- ABC of labour care: Care of the newborn in the delivery room. *BMJ* 1999;318:1403-1406.
- ABC of labour care: Obstetric emergencies. *BMJ* 1999;318:1342-1345.
- ABC of labour care: Operative delivery. *BMJ* 1999;318:1260-1264.
- ABC of labour care: Induction. *BMJ* 1999;318:995-998.
- ABC of labour care: Labour in special circumstances. *BMJ* 1999;318:1124-1127.
- ABC of labour care: Physiology and management of normal labour. *BMJ* 1999;318:793-796.
- ABC of labour care: Place of birth. *BMJ* 1999;318:721-723.
- ABC of labour care: Preterm labour and premature rupture of membranes. *BMJ* 1999;318:1059-1062.
- ABC of labour care: Relief of pain. *BMJ* 1999;318:927-930.
- ABC of labour care: Unusual presentations and positions and multiple pregnancy. *BMJ* 1999; 318:1192-1194.
- Alfirevic Z. Oral misoprostol for induction of labour (Cochrane Review). *The Cochrane Library* 2002;Issue 2.
- Alfirevic Z, Devane D, Gyte GM. Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour. *Cochrane DB Syst Rev* 2006;3:CD006066.
- Antenatal Corticosteroid Therapy for Fetal Maturation. SOGC clinical practice guidelines policy statement. December 1995:53.
- Baskett, T. Essential management of obstetric emergencies, 3rd ed. Bristol: Clinical Press, 1999.
- Bastian LA, Piscitelli JT. Is this patient pregnant? Can you reliably rule in or rule out early pregnancy by clinical examination? *JAMA* 1997;278:586-591.
- Berghella V, et al. Cerclage for prevention of preterm birth in women with a short cervix found on transvaginal examination: a randomized trial. *Amer J Obs Gyn* 2004;191:1311-1317.
- Berghella V, Rafael TJ, Szychowski JM, Rust OA, Owen J. Cerclage for short cervix on ultrasonography in women with singleton gestations and previous preterm birth: a meta-analysis. *Obstet Gynecol* 2011;117:663-671.
- Boucher M. Mode of delivery for pregnant women infected by the human immunodeficiency virus. SOGC Clinical Practice Guidelines. April 2001:101.
- Boucher M, Gruslin A. The reproductive care of women living with hepatitis C infection. SOGC Clinical Practice Guidelines. October 2000:96.
- Bricker L, Luckas M. (2002). Amniotomy alone for induction of labour (Cochrane Review). *The Cochrane Library* 2002;Issue 2.
- Carol, Blenning. An approach to the postpartum office visit. *Am Fam Physician* 2005;72:2491-2496.
- Carroll G, Mignini L. Episiotomy for vaginal birth. *Cochrane DB Syst Rev* 2009;1:CD000081.
- Carroll JC, Reid AJ, Biringe A, et al. Effectiveness of the antenatal psychosocial health assessment (ALPHA) form in detecting psychosocial concerns: a randomized controlled trial. *CMAJ* 2005;173:253-259.
- Centers for Disease Control and Prevention. prevention of perinatal group B streptococcal disease. *MMWR* 2010;59(No.RR-10).
- Chodirker et al. Canadian guidelines for prenatal diagnosis part 1 and part 2. SOGC Clinical Practice Guidelines. July 2001 and June 2000. No105.
- Chyu JK, Strassner HT. Prostaglandin E2 for cervical ripening: a randomized comparison of cervidil vs. prepilid. *AMJ Obstet Gynecol* 1997;177:606-611.
- Cohen-Kerem R, Nulman I, Abramow-Newerly M, Medina D, Maze R, Brent RL, Koren G. Diagnostic radiation in pregnancy: perception versus true risks. *J Obstet Gynaecol Can* 2005;28:43-48.
- Crane, J. Induction of labour at term. SOGC Clinical Practice Guideline 2001;107:1-12.
- Fetal health Surveillance in Labour – part 1 and part 2. SOGC Clinical Practical Guideline. January 1996. p45.
- Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. *Rev Obstet Gynecol* 2009;2:76-83.
- Gagnon A, Wilson R. Obstetrical complications associated with abnormal maternal serum markers analytes. SOGC Clinical Practice Guidelines. 2008;216:918-932.
- Goldenberg et al. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75-84.
- Guise JM, Berlin M, McDonagh M, Osterweil P, Chan B, Helfand M. Safety of vaginal birth after cesarean: a systematic review. *Obstet Gynec* 2004;103:420-429.
- Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. *Cochrane DB Syst Rev* 2007;1:CD000324.
- Hannah, M. Post-term pregnancy. SOGC Clinical Practice Guidelines Committee Opinion. March 1997. p15.
- Hennessey MH, Rayburn WF, Stewart JD, Likes EC. Preeclampsia and induction of labour: a randomized comparison of prostaglandin E2 as an intracervical gel, with oxytocin immediately, or as a sustained – release vaginal insert. *AMJ Obstet Gynecol* 1998;179:1204-1209.
- Hod M, Bar J, Peled Y, Fried S, Katz I, Itzhak M, Ashkenazi S, Schindler B, Ben-Rafael Z. Antepartum management protocol. Timing and mode of delivery in gestational diabetes. *Obstet Gynecol* 2009;113:206-217.
- Hodnett ED, Gates S, Hofmeyr GJ, Sakala C, Weston J. Continuous support for women during childbirth. *Cochrane DB Syst Rev* 2011;2:CD003766.
- Howarth GR, Botha DJ. Amniotomy plus intravenous oxytocin for induction of labour (Cochrane Review). *The Cochrane Library* 2002;Issue 2.
- Kelly AJ, Tan B. Intravenous oxytocin alone for cervical ripening and induction of labour (Cochrane Review). *The Cochrane Library* 2002;Issue 2.
- Kent, N. Prevention and treatment of venous thromboembolism (VTE) in obstetrics. SOGC Clinical Practice Guidelines. September 2000. p95.
- Koren, G. Motherisk update: Caffeine during pregnancy? *Canadian Family Phys* 2000;46:801-803.
- Kotaska et al. Vaginal delivery of breech presentation. SOGC Clinical Practice Guidelines. 2009;226:557-566.
- Langlois S, Ford J, and Chitayat D. Carrier screening for thalassemia and hemoglobinopathies in Canada. SOGC Technical Update 2008;217:950-959.
- Langlois S, Wilson R. Carrier screening for genetic disorders in individuals of ashkenazi jewish descent. SOGC Clinical Practice Guidelines. 2006;177:324-332.
- Ling, F. and Duff, P. Obstetrics and Gynecology, Principles for practice. USA: McGraw-Hill Companies, 2002.
- Lowder LJ, Burrows LJ, Krohn MA, Weber AM. Risk factors for primary and subsequent anal sphincter lacerations: a comparison of cohorts by parity and prior mode of delivery. *Am J Obstet Gynecol* 2007;196:344.e1-5.
- Luckas M, Bricker L. Intravenous prostaglandin for induction of labour (Cochrane Review). *The Cochrane Library* 2000;Issue 2.
- Magee LA, Helewa M, Moutquin J-M, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *JOGC* 2008;30:S1.
- Meltwer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, Yale JF, Zinman B, Lillie D. 1998 Clinical practice guidelines for the management of diabetes in Canada. *CMAJ* 1998;159(B suppl):S1-29.
- Menezes EV, Yakob MY, Soomro T, Haws RA, Darmstadt GL, Bhutta ZA. Reducing stillbirths: prevention and management of medical disorders and infections during pregnancy. *BMC Pregnancy Childbirth*. 2009;9(Suppl 1):S4.
- Ministry of Health and Long Term Care and Canadian Medical Association. Antenatal record 1. Ontario.
- Ministry of Health and Long Term Care and Canadian Medical Association. Antenatal record 2. Ontario.
- Money, D and Dobson, S. The prevention of early-onset group B streptococcal disease. SOGC Clinical Practice Guidelines. 2004.
- Mount Sinai Hospital. First trimester combined screening program. 2001.
- North York General Hospital Genetics Program. Integrated prenatal screening. 1999.
- Ottinyer WS, Menara MK, Brost BC. A randomized control trial of prostaglandin E2 intracervical gel and a slow release vaginal for preinduction cervical ripening. *AMJ Obstet Gynecol* 1998;179:349-353.
- Schrag SJ, Zell ER, Lynfield R, Roome A, Arnold KE, Craig AS, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *NEJM* 2002;347:233-239.
- Schuermans, N., MacKinnon, C., Lane C., Etches, D. Prevention and management of postpartum hemorrhage. SOGC Clinical Practice Guidelines. 2000. p88.
- SOGC. Clinical Practical Guidelines. Guidelines for exercise in pregnancy. Committee Opinion. June 2003.
- SOGC. Fetal health surveillance: antepartum and intrapartum consensus guideline. 2007.
- SOGC. Conservative management of urinary incontinence. 2006. p186.
- SOGC. Healthy beginnings: guidelines for care during pregnancy and childbirth. Clinical Practice Guidelines Policy Statement. December 1998: 71.
- SOGC. Guidelines for the management of nausea and vomiting in pregnancy. Clinical Practice Guidelines Committee Opinion. November 1995. p12.
- SOGC. Midurethral minimally invasive sling procedures for stress urinary incontinence. 2008. p213.
- Statistics Canada. Induced Abortion Statistics. 2005:82-223-XWE. p16.
- Stewart, D. A broader context for maternal mortality. *CMAJ* 2006;74:302-303.
- Stewart JD, Rayburn WF, Farmer KC, Ciles EM, Schipaul AH Jr, Stanley JR. Effectiveness of prostaglandin E2 intracervical gel (prepidil) with immediate oxytocin vs. vaginal insert (cervidil) for induction of labour. *AMJ Obstet Gynecol* 1998;179:1175-1180.
- Summers A, Langlois S, Wyatt P, Wilson D. Prenatal screening for fetal aneuploidy. SOGC Clinical Practice Guidelines. 2007;187:146-161.
- Van den Hof, M. and Crane, J. Ultrasound cervical assessment in predicting preterm birth. SOGC Clinical Practice Guidelines. May 2001. p102.
- Zhany et al. *Obstet Gynecol* 1993;82:306-312.



Harleen Bedi and Yao Wang, chapter editors  
Jieun Kim and Daniel Soong, associate editors  
Jeff Martin, EBM editor  
Dr. Wai-Ching Lam and Dr. Marisa Sit, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Retina</b> . . . . .	<b>23</b>
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	Central Retinal Artery Occlusion (CRAO)	
<b>Differential Diagnoses of Common Presentations</b> . . . . .	<b>3</b>	Branch Retinal Artery Occlusion (BRAO)	
Loss of Vision	Diplopia	Central/Branch Retinal Vein Occlusion (CRVO/BRVO)	
Red Eye	Ocular Problems in the Elderly	Retinal Detachment (RD)	
Ocular Pain	Ocular Problems in the	Retinitis Pigmentosa	
Floater	Contact Lens Wearer	Leber's Congenital Amaurosis	
Flashes of Light	Acute Painless Vision Loss	Age-Related Macular Degeneration (ARMD)	
Photophobia			
<b>Ocular Emergencies</b> . . . . .	<b>5</b>	<b>Glaucoma</b> . . . . .	<b>27</b>
<b>The Ocular Examination</b> . . . . .	<b>5</b>	Primary Open Angle Glaucoma (POAG)	
<b>Optics</b> . . . . .	<b>8</b>	Normal Tension Glaucoma	
<b>Imaging Modalities</b> . . . . .	<b>9</b>	Secondary Open Angle Glaucoma	
<b>The Orbit</b> . . . . .	<b>10</b>	Primary Angle-Closure Glaucoma	
Globe Displacement	Orbital Cellulitis	Secondary Angle-Closure Glaucoma	
Preseptal Cellulitis			
<b>Lacrimal Apparatus</b> . . . . .	<b>11</b>	<b>Pupils</b> . . . . .	<b>30</b>
Dry Eye Syndrome	Dacryocystitis	Pupillary Light Reflex	
Epiphora (Tearing)	Dacryoadenitis	Pupil Abnormalities	
		Dilated Pupil (Mydriasis)	
		Constricted Pupil (Miosis)	
		Relative Afferent Pupillary Defect (RAPD)	
<b>Lids and Lashes</b> . . . . .	<b>12</b>	<b>Malignancies</b> . . . . .	<b>34</b>
Lid Swelling	Hordeolum (Stye)	Lid Carcinoma	
Ptosis	Chalazion	Malignant Melanoma	
Trichiasis	Blepharitis	Metastases	
Entropion	Xanthelasma		
Ectropion		<b>Ocular Manifestations of Systemic Disease</b> . . . . .	<b>35</b>
<b>Conjunctiva</b> . . . . .	<b>14</b>	HIV/AIDS	
Pinguecula		Other Systemic Infections	
Pterygium		Diabetes Mellitus (DM)	
Subconjunctival Hemorrhage		Hypertension	
Conjunctivitis		Multiple Sclerosis (MS)	
		TIA/Amaurosis Fugax	
		Graves' Disease	
		Connective Tissue Disorders	
		Giant Cell Arteritis (GCA)/Temporal Arteritis	
		Sarcoidosis	
<b>Sclera</b> . . . . .	<b>16</b>	<b>Pediatric Ophthalmology</b> . . . . .	<b>38</b>
Episcleritis	Scleritis	Strabismus	
		Amblyopia	
<b>Cornea</b> . . . . .	<b>17</b>	Leukocoria	
Foreign Body	Herpes Zoster	Retinoblastoma	
Corneal Abrasion	Keratoconus	Retinopathy of Prematurity (ROP)	
Recurrent Erosions	Arcus Senilis	Nasolacrimal System Defects	
Corneal Ulcer	Kayser-Fleischer Ring	Ophthalmia Neonatorum	
Herpes Simplex		Congenital Glaucoma	
<b>The Uveal Tract</b> . . . . .	<b>20</b>	<b>Ocular Trauma</b> . . . . .	<b>42</b>
Uveitis		Blunt Trauma	Blow-Out Fracture
		Penetrating Trauma	Chemical Burns
		Hyphema	
<b>Lens</b> . . . . .	<b>21</b>	<b>Surgical Ophthalmology</b> . . . . .	<b>44</b>
Cataracts		<b>Ocular Drug Toxicity</b> . . . . .	<b>44</b>
Dislocated Lens (Ectopia Lentis)		<b>Common Medications</b> . . . . .	<b>44</b>
		<b>References</b> . . . . .	<b>46</b>
<b>Vitreous</b> . . . . .	<b>22</b>		
Posterior Vitreous Detachment (PVD)			
Vitreous Hemorrhage			
Endophthalmitis and Vitritis			

## Acronyms

(BC) VA	(best corrected) visual acuity	GAT	Goldmann applanation tonometry	POAG	primary open angle glaucoma
AION	anterior ischemic optic neuropathy	GCA	giant cell arteritis	PRK	photorefractive keratectomy
ARMD	age-related macular degeneration	HRT	Heidelberg retinal tomography	PVD	posterior vitreous detachment
BRAO	branch retinal artery occlusion	INO	internuclear ophthalmoplegia	RA	rheumatoid arthritis
BRVO	branch retinal vein occlusion	IOL	intraocular lens	RAPD	relative afferent pupillary defect
C:D	cup to disc ratio	IOP	intraocular pressure	RD	retinal detachment
CMV	cytomegalovirus	LASIK	laser-assisted in situ keratomileusis	ROP	retinopathy of prematurity
CRAO	central retinal artery occlusion	OHT	ocular hypertension	RPE	retinal pigment epithelium
D	diopter	PACG	primary angle-closure glaucoma	SLE	systemic lupus erythematosus
DR	diabetic retinopathy	PDR	proliferative diabetic retinopathy	SPK	superficial punctate keratitis
EOM	extraocular movement	PDT	photodynamic therapy	VEGF	vascular endothelial growth factor
FML	fluoromethalone	PERLA	pupils equal, round, and reactive to light and accommodation	YAG	Yttrium aluminium garnet

## Basic Anatomy Review

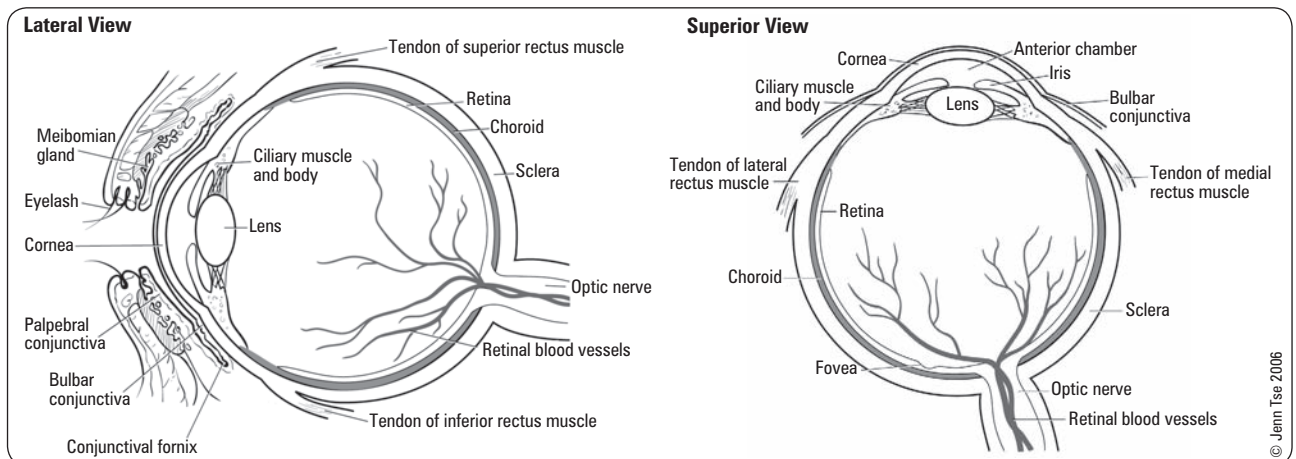


Figure 1. Anatomy of the eye

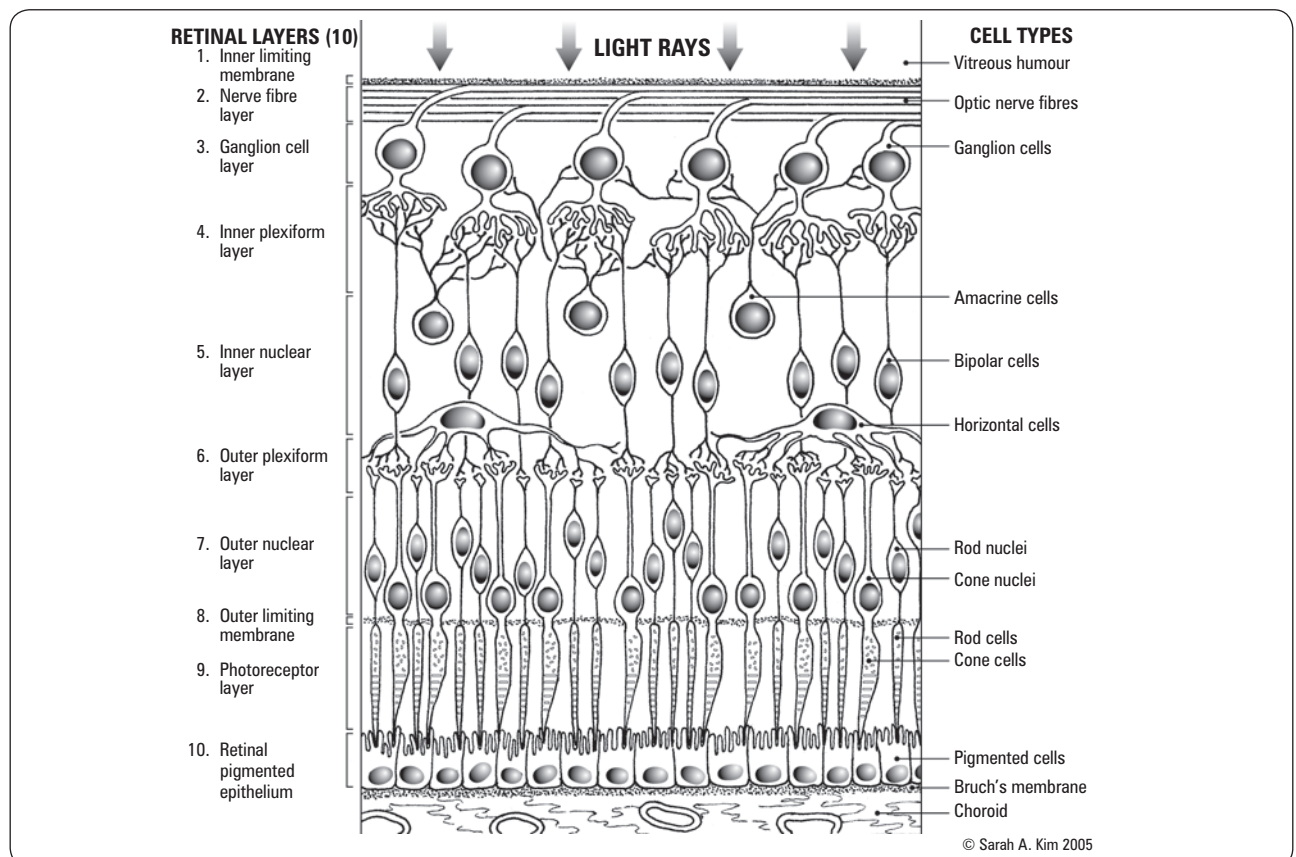


Figure 2. Layers of the retina

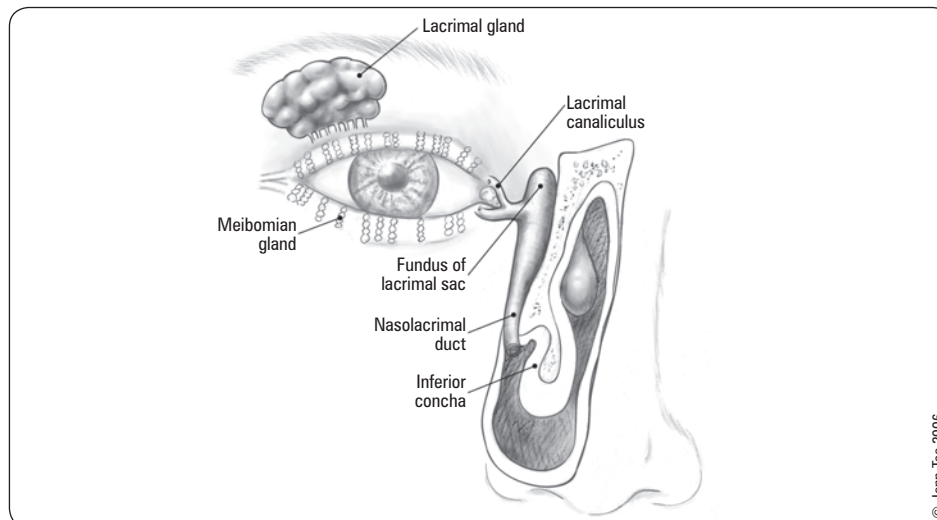
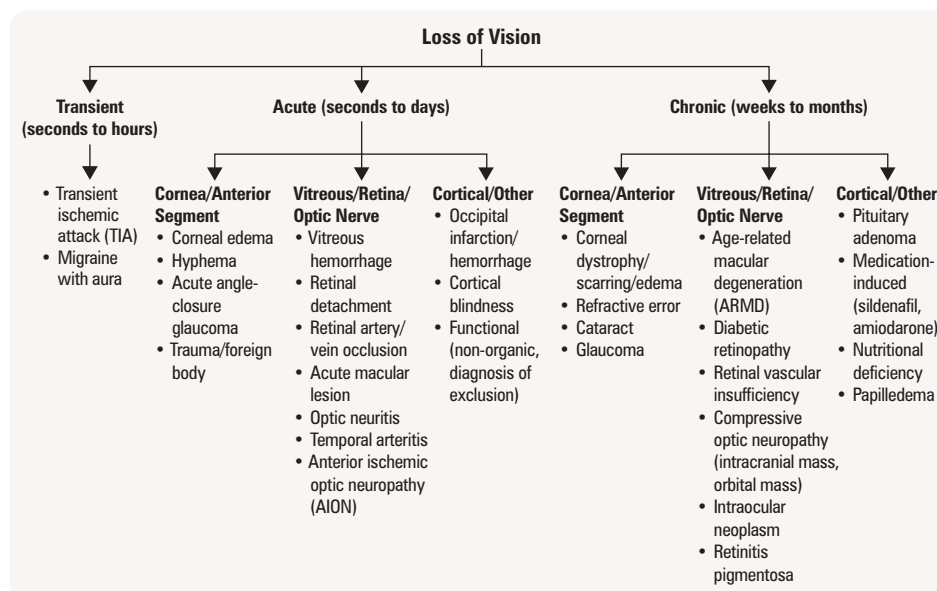


Figure 3. Tear drainage from the eye (lacrimal apparatus)

## Differential Diagnoses of Common Presentations



### Loss of Vision



#### Top 3 DDx of Acute Loss of Vision

- Trauma/foreign body
- Retinal artery/vein occlusion
- Retinal detachment



#### Top 3 DDx of Chronic Loss of Vision

- Reversible**
  - Cataract
  - Refractive error
  - Corneal dystrophy

- Irreversible**
  - ARMD
  - Glaucoma
  - Diabetic retinopathy

Note: Anti-VEGF treatment for exudative ARMD and diabetic macular edema may reverse some vision loss.

Figure 4. Loss of vision

## Red Eye



- lids/orbit/lacrimal system
  - hordeolum/chalazion
  - blepharitis
  - entropion/ectropion
  - foreign body/laceration
  - dacryocystitis/dacryoadenitis
- conjunctiva/sclera
  - subconjunctival hemorrhage
  - conjunctivitis
  - dry eyes
  - pterygium
  - episcleritis/scleritis
  - preseptal/orbital cellulitis
- cornea
  - foreign body (including contact lens)
  - keratitis
  - abrasion, laceration
  - ulcer
- anterior chamber
  - anterior uveitis (iritis, iridocyclitis)
  - acute angle-closure glaucoma
  - hyphema (blood in anterior chamber)
  - hypopyon (pus in anterior chamber)
- other
  - trauma
  - post-operative
  - endophthalmitis

## Ocular Pain

- differentiate from eye fatigue (asthenopia)
- herpes zoster prodrome
- trauma/foreign body
- keratitis
- corneal abrasion, corneal ulcer
- acute angle-closure glaucoma
- acute uveitis
- scleritis, episcleritis
- optic neuritis

## Floaters

- age-related vitreous syneresis (shrinkage and collapse of vitreous gel)
- posterior vitreous detachment (PVD)
- vitreous hemorrhage
- retinal tear/detachment
- posterior uveitis

## Flashes of Light (Photopsia)

- PVD
- retinal tear/detachment
- migraine with aura

## Photophobia (Severe Light Sensitivity)

- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis, encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

## Diplopia (Double Vision)



- binocular diplopia (occurs with both eyes open, eliminated with occlusion of either eye)
  - strabismus, CN palsy (III, IV, VI) 2° to ischemia, diabetes, tumour, trauma, myasthenia gravis, muscle restriction/entrapment, thyroid ophthalmopathy, internuclear ophthalmoplegia (INO) 2° to multiple sclerosis, brainstem infarct
- monocular diplopia (occurs with one eye open, remains with occlusion of unaffected eye)
  - refractive error, strands of mucus in tear film, keratoconus, cataracts, dislocated lens, peripheral iridotomy

## Ocular Problems in the Elderly

- blepharitis
- ptosis
- entropion, ectropion
- dry eyes, epiphora (excessive tearing)
- presbyopia
- cataracts
- glaucoma
- age-related macular degeneration
- retinal artery/vein occlusion
- temporal arteritis (arteritic ischemic optic neuropathy)

## Ocular Problems in the Contact Lens Wearer

- superficial punctate keratitis (SPK) from dry eyes
- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis/contact lens allergy
- sterile corneal infiltrates (immunologic)
- infected ulcers (*Pseudomonas*, *Acanthamoeba*)

## Acute Painless Vision Loss



- vitreous hemorrhage
- retinal artery/vein occlusion
- retinal detachment
- anterior ischemic optic neuropathy (AION)
- optic neuritis
- amaurosis fugax

Table 1. Common Differential Diagnoses of Red Eye

	Conjunctivitis	Acute Iritis	Acute Angle-Closure Glaucoma	Keratitis (Corneal Abrasion/Ulcer)
<b>Discharge</b>	Bacteria: purulent Virus: serous Allergy: mucous	No	No	Profuse tearing
<b>Pain</b>	No	++ (tender globe)	+++ (nausea)	++ (on blinking)
<b>Photophobia</b>	No	+++	+	++
<b>Blurred Vision</b>	No	++	+++	Varies
<b>Pupil</b>	Normal	Smaller	Fixed in mid-dilation	Same or smaller
<b>Injection</b>	Conjunctiva with limbal pallor	Ciliary flush	Diffuse	Diffuse
<b>Cornea</b>	Normal	Keratic precipitates	Cloudy	Infiltrate, edema, epithelial defects
<b>Intraocular pressure</b>	Normal	Varies	Increased markedly	Normal or increased
<b>Anterior chamber</b>	Normal	+++ Cells and flare	Shallow	Cells and flare or normal
<b>Other</b>	Large, tender pre-auricular node(s) if viral	Posterior synechiae	Coloured halos Nausea and vomiting	



Not every red eye has conjunctivitis.

## Ocular Emergencies

These require urgent consultation to an ophthalmologist for management

### Sight Threatening

- lid/globe lacerations
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute angle-closure glaucoma
- CRAO
- intraocular foreign body
- retinal detachment (especially when macula threatened)
- endophthalmitis

### Life Threatening

- proptosis (r/o cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or neoplastic lesion)
- papilledema (must r/o intracranial mass lesion)
- orbital cellulitis
- temporal (giant cell) arteritis
- leukocoria: white reflex (absent red reflex, must rule out retinoblastoma)

## The Ocular Examination

### Visual Acuity – Distance

- Snellen Acuity (Figure 5) =  $\frac{\text{testing distance (usually 20 feet or 6 metres)}}{\text{smallest line patient can read on the chart}}$ 
  - e.g. 20/40 = what the patient can see at 20 feet (numerator), what a “normal” person can see at 40 feet (denominator)
- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
- legal blindness is BCVA that is  $\leq 20/200$  in best eye
- minimum visual requirements to operate a non-commercial automobile in Ontario are: with both eyes open and examined together, 20/50 BCVA

### Visual Acuity – Near

- use pocket vision chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance VA possible (e.g. immobile patient, no distance chart available)

### Example 1

SC  
V 20/40 -1  
20/80 +2 → 20/25 PH

### Example 2

CC  
V CF 3'  
HM

**Note:** RIGHT EYE visual acuity always listed on top.

V Vision  
SC Without correction  
CC With correction  
20/40 -1 All except one letter of 20/40  
20/80 +2 All of 20/80 plus two letters of 20/70  
PH Visual acuity with pinhole correction  
CF Counting fingers  
HM Hand motion

Figure 5. Ophthalmology nomenclature for VA



OD = oculus dexter = right eye  
OS = oculus sinister = left eye  
OU = oculus uterque = both eyes



Snellen visual acuity of 20/20 equates to “normal” vision.



### Normal Infant and Child Visual Acuity

- 6-12 mo: 20/120
- 1-2 yr: 20/80
- 2-4 yr: 20/20



### Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics

- newborns
  - VA cannot be tested
- 3 mo-3 yr (can only assess visual function, not acuity)
  - test each eye for fixation symmetry using an interesting object
  - normal function noted as "CSM" = central, steady, and maintained
- 3 yr until alphabet known
  - pictures or letter cards/charts such as HOTV or Sheridan-Gardner test (children point to optotypes on a provided matching card)
  - tumbling "E" chart

### Colour Vision

- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye, specify incorrect plates
- important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
- note: red-green colour blindness is sex-linked and occurs in 7-10% of males

### VISUAL FIELDS

- test "visual fields by confrontation" (4 quadrants, each eye tested separately) for estimation of visual field loss (Figure 6)
- accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- use Amsler grid (each eye individually) to test for central or paracentral scotomas (island-like gaps in the vision) in patients with ARMD

### PUPILS

- use reduced room illumination with patient focusing on distant object to prevent "near reflex"
- examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
- test for relative afferent pupillary defect (RAPD) with swinging flashlight test
- test pupillary constriction portion of near reflex by bringing object close to patient's nose
- "normal" pupil testing often noted as PERLA (pupils equal, round, and reactive to light and accommodation)

### ANTERIOR CHAMBER DEPTH

- shine light tangentially from temporal side
- if >2/3 of nasal side of iris in shadow → shallow anterior chamber

### The van Herick method

- shine thin angled slit beam onto the peripheral cornea of each eye
- estimate depth between the posterior surface of the cornea and the iris as a proportion of corneal thickness
- follow-up with gonioscopy for ratios  $\leq 1/4$

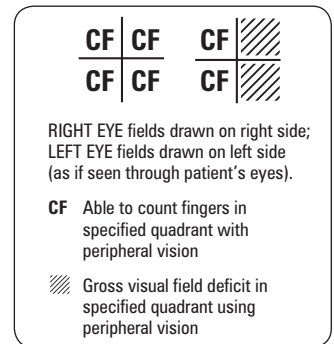
### Gonioscopy

- allows direct visualization of the angle structures
- angle considered open if trabecular meshwork, scleral spur, and iris processes are visualized
- angle considered narrow (occludable) if only *Schwalbe's* line or a small portion of the trabecular meshwork is seen

### EXTRAOCULAR MUSCLES

#### Alignment

- Hirschberg corneal reflex test
  - examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  - shine light into patient's eyes from ~30 cm away
  - corneal light reflex should be symmetric and at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see *Strabismus*, OP38)



**Figure 6. Ophthalmology nomenclature for visual fields by confrontation**



For patients with dark irides, test pupils using an ophthalmoscope focused on the red reflex. This will provide a better view than using a penlight.



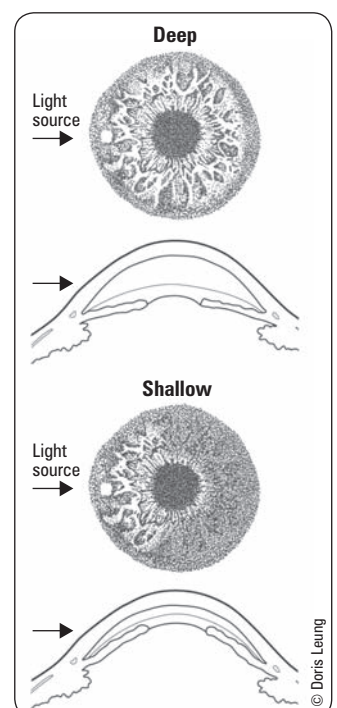
#### Ocular Changes for Near Fixation

- Eye convergence
- Pupil constriction
- Lens accommodation



#### 4 Ps of InsPection

**Pupil:** shape, size, symmetry  
**Position:** esotropia, exotropia, central  
**Ptosis**  
**Primary nystagmus**



**Figure 7. Estimation of anterior chamber depth**



## Movement

- examine movement of eyeball through six cardinal positions of gaze (Figure 8)
- ask patient if diplopia is present in any position of gaze
- observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end-gaze is usually normal
- see sidebar for cranial nerve innervation of extraocular muscles

## Diplopia

- major symptom associated with dysfunction of extraocular muscles or abnormalities of the motor nerves innervating these muscles
- must determine whether diplopia is monocular or binocular
- determine whether diplopia was sudden onset (due to an acute event such as ischemia) or gradual (due to progressive process such as tumour or inflammation)
- with myasthenia gravis, diplopia and ptosis usually worsen on prolonged upgaze; can rule out with a Tensilon® test (see [Neurology](#), N32)
- if suspect compressive lesion (most commonly seen with CN III palsy with a blown pupil), need MRI and angiography to rule out aneurysm or tumour
- new-onset diplopia that disappears with occlusion of either eye (binocular diplopia) needs urgent referral while chronic binocular diplopia and monocular diplopia should be referred non-urgently

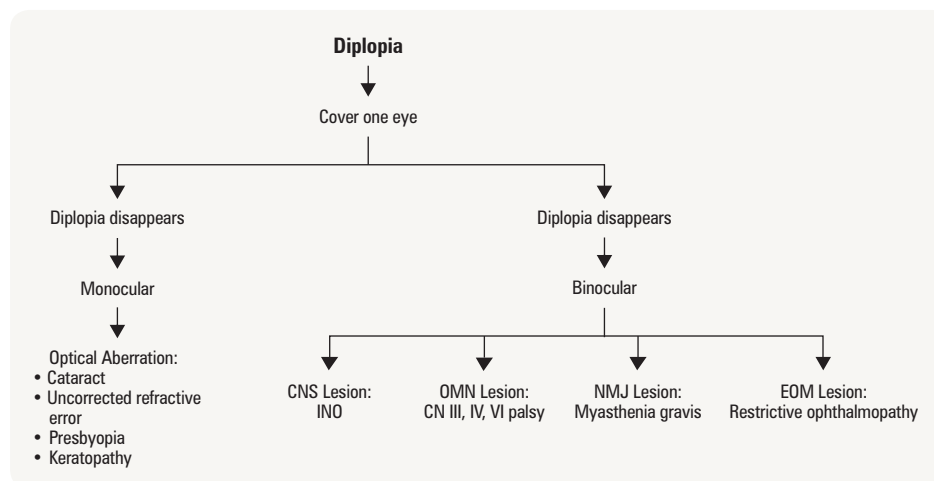


Figure 9. Diplopia

## EXTERNAL EXAMINATION

- four Ls
  - lymph nodes (preauricular, submandibular)
  - lids
  - lashes
  - lacrimal system

## SLIT-LAMP EXAMINATION

- systematically examine all structures of the anterior segment and anterior vitreous (for structures see Figure 1)
- when necessary, use:
  - fluorescein dye: stains Bowman's membrane in de-epithelialized cornea; dye appears green with cobalt blue filtered light
  - Rose Bengal dye: stains devitalized corneal epithelium
- special lenses (78 or 90 D) used with the slit-lamp allow a binocular, stereoscopic view of the fundus and vitreous

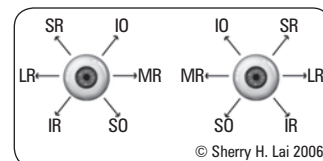


Figure 8. Diagnostic positions of gaze for isolated primary actions of extraocular muscles



### Extraocular Muscle Innervations

LR6 SO4 AE3

Lateral Rectus via CN VI

Superior Oblique via CN IV

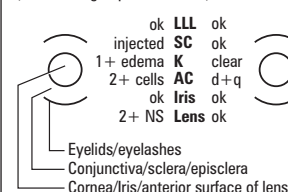
All Else via CN III (superior, medial, and inferior rectus, inferior oblique)



### Aqueous Flare

- Resembles dust particles in a beam of light
- Results from protein leaking from blood vessels
- Distinguish from aqueous cells (individual cells in anterior chamber)

**Note:** RIGHT EYE drawn on the left, LEFT EYE drawn on the right (as if looking at patient's face).



- LLL Lids, lashes, lacrimal
- SC Sclera, conjunctiva
- K Cornea
- AC Anterior chamber
- d+q Deep (not shallow) and quiet (no cells in AC)
- NS Nuclear sclerosis (cataract)

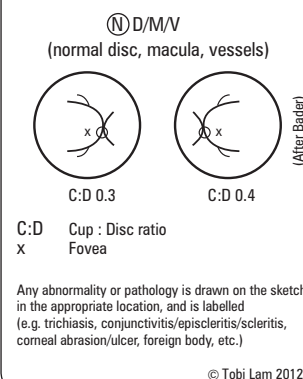


Figure 10. Slit-lamp examination note

## TONOMETRY

- measurement of intraocular pressure (IOP) (Figure 11)
- normal range is 10-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by:
  - Goldmann applanation tonometry (GAT): gold standard, performed using the slit-lamp with special tip (prism)
  - Tono-Pen®: benefit is portability and use of disposable probe tips. Use when cornea is scarred/asymmetric (GAT inaccurate)
  - air puff (non-contact and least reliable)
- use topical anesthetic for GAT and Tono-Pen®

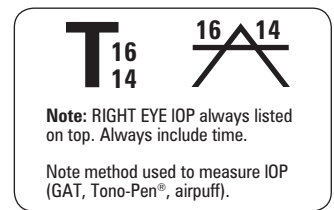


Figure 11. Tonometry

## OPHTHALMOSCOPY/FUNDOSCOPY

- performed with:
  - direct ophthalmoscope (monocular with small field of view, only posterior pole visualized)
  - slit-lamp with 78 or 90 D lens (binocular view, visualization to mid-periphery of retina)
  - indirect ophthalmoscopy with headlamp and 20 or 28 D lens (binocular view, visualization of entire retina to ora serrata/edge of retina)
- best performed with pupils dilated (see Table 11 for list of mydriatics and cycloplegics)
  1. assess red reflex
    - ♦ light reflected off the retina produces a “red reflex” when viewed from ~1 foot away
    - ♦ anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract)
  2. examine the posterior segment of the eye (Figure 10)
    - ♦ vitreous
    - ♦ optic disc (colour, C:D ratio, sharpness of disc margin)
    - ♦ macula (~2 disc diameters temporal to disc), fovea (foveal light reflex)
    - ♦ retinal vessels
    - ♦ retinal background
- contraindications to pupillary dilatation
  - shallow anterior chamber – can precipitate acute angle-closure glaucoma
  - iris-supported anterior chamber lens implant
  - potential neurologic abnormality requiring pupil evaluation
  - use caution with cardiovascular disease – mydriatics may cause tachycardia



### Central Corneal Thickness (CCT)

Average CCT = 550 µm

By GAT, IOP is over estimated with thick corneas and under estimated with thin corneas.

### Desired Myers Pattern on GAT



Note: Thick Myers overestimate the IOP and are a result of excess fluorescein



### Quick Tips for Direct Ophthalmoscopy

- Examine in a dark room
- Ask patient to focus on a distant object
- Match ophthalmoscope light aperture to size of pupil (i.e. smaller aperture for undilated eye)
- Use moderate light intensity
- Use your left/right eye and hand to examine patient's left/right eye respectively
- Get in close! Proximity to patient's eye is key. You may rest your hand on the patient's cheek



### Structures Responsible for Refractive Power

- Cornea (2/3)
- Lens (1/3)



### Myopia

LMN

Long globe

Myopic

Negative correction/Nearsighted

# Optics

## REFRACTION

- two techniques used
  - flash/streak retinoscopy: refractive error determined objectively by the examiner using lenses and retinoscope
  - manifest: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
- a typical lens prescription would contain:
  - sphere power in D (measurement of refractive power of lens, equal to reciprocal of focal length in meters)
  - cylinder power in D to correct astigmatism (always positive value)
  - axis of cylinder in degrees
  - “add” (bifocal/progressive reading lens) for presbyopes
  - e.g. -1.50 + 1.00 x 120 degrees, add +2.00

## REFRACTIVE EYE SURGERY

- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK and LASIK (see *Surgical Ophthalmology*, OP44)
- potential risks/side-effects: infection, under/overcorrection, decreased night vision (nyctalopia), corneal haze, dry eyes, regression, complete sever of corneal flap (LASIK only)

Table 2. Optics

	Pathophysiology	Clinical Features	Treatment	Complications
<b>Emmetropia</b>	<ul style="list-style-type: none"> <li>Image of distant objects focus exactly on the retina (Figure 12)</li> </ul>	<ul style="list-style-type: none"> <li>No refractive error</li> </ul>		
<b>Myopia</b>	<ul style="list-style-type: none"> <li>Globe too long relative for refractive mechanisms, or refractive mechanisms too strong</li> <li>Light rays from distant object focus in front of retina → blurring of (distance) vision (Figure 12)</li> </ul>	<ul style="list-style-type: none"> <li>"Nearsightedness"</li> <li>Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with diabetes or cataracts</li> <li>Blurring of distance vision; near vision usually unaffected</li> <li>Prevalence: 30-40% in U.S. population</li> </ul>	<ul style="list-style-type: none"> <li>Correct with negative diopter/concave/"negative" lenses to diverge light rays</li> <li>Refractive eye surgery</li> </ul>	<ul style="list-style-type: none"> <li>Retinal tear/detachment, macular hole, open angle glaucoma</li> <li>Other complications that are not prevented with refractive correction</li> </ul>
<b>Hyperopia</b>	<ul style="list-style-type: none"> <li>Globe too short relative to refractive mechanisms, or refractive mechanisms too weak</li> <li>Light rays from distant object focus behind retina → blurring of near ± distant vision (Figure 12)</li> <li>May be developmental or due to any etiology that shortens globe</li> </ul>	<ul style="list-style-type: none"> <li>"Farsightedness"</li> <li>Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia (see <i>Strabismus</i>, OP38)</li> <li>30s-40s: blurring of near vision due to decreased accommodation, may need reading glasses</li> <li>&gt;50s: blurring of distance vision due to severely decreased accommodation</li> </ul>	<ul style="list-style-type: none"> <li>When symptomatic, correct with positive diopter/convex/"plus" lenses to converge light rays</li> <li>Refractive eye surgery</li> </ul>	<ul style="list-style-type: none"> <li>Angle-closure glaucoma, particularly later in life as lens enlarges</li> </ul>
<b>Astigmatism</b>	<ul style="list-style-type: none"> <li>Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped)</li> <li>Two types: <ul style="list-style-type: none"> <li>Regular – curvature uniformly different in meridians at right angles to each other</li> <li>Irregular – distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Affects approximately 30% of population, with prevalence increasing with age</li> <li>Mild astigmatism unnoticeable</li> <li>Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches</li> </ul>	<ul style="list-style-type: none"> <li>Correct with cylindrical lens (if regular), try contact lens (if irregular)</li> <li>Refractive eye surgery</li> </ul>	
<b>Presbyopia</b>	<ul style="list-style-type: none"> <li>Normal aging process (&gt;40 yr)</li> <li>Hardening/reduced deformability of lens results in decreased accommodative ability</li> <li>Accommodative power is 14D at age 10, diminishes to 3.5D by age 40</li> <li>Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia)</li> </ul>	<ul style="list-style-type: none"> <li>If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected</li> <li>If initially myopic, person removes distance glasses to read</li> <li>If initially hyperopic, symptoms of presbyopia occur earlier</li> </ul>	<ul style="list-style-type: none"> <li>Correct with positive diopter/convex/"plus" lenses for reading</li> </ul>	
<b>Anisometropia</b>	<ul style="list-style-type: none"> <li>Difference in refractive errors between eyes</li> </ul>			<ul style="list-style-type: none"> <li>Second most common cause of amblyopia in children</li> </ul>

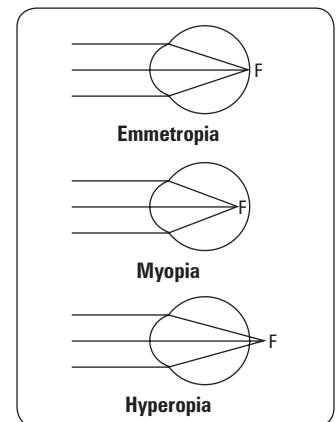


Figure 12. Emmetropia and refractive errors

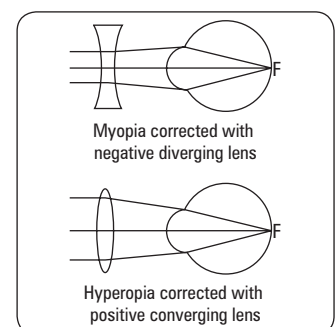


Figure 13. Correction of refractive errors

## Imaging Modalities

- **adaptive optics scanning laser ophthalmology – optical coherence tomography (SLO-OCT)**
  - combines the surface detail of confocal ophthalmoscopy with the internal detail of OCT
  - allows 3D OCT images, volume and area maps, and retinal thickness maps, at the resolution of living rods and cones
  - can visualize photoreceptors, nerve fibres and blood cells in retinal capillaries
- **CT, MRI**
  - orbital imaging, particularly in orbital trauma and neuro-ophthalmology
- **fluorescein angiography**
  - non-invasive evaluation of vascular pattern of the fundus
  - commonly used in ARMD, DR, retinal vascular diseases
- **indocyanine green angiography**
  - uses infra-red light and intravenous ICG dye for imaging of choroidal structure
  - particularly useful to detect polypoidal vasculopathy (variant of ARMD) more commonly present among Asian patients

- **Heidelberg retinal tomograph (HRT)**
  - confocal scanning laser tomography of retinal nerve head and surrounding nerve fibre layer
  - used to assess extent of structural glaucomatous changes
- **optical coherence tomography (OCT)**
  - non-invasive, cross-sectional, high-resolution imaging of vitreous, retinal layers, optic nerve
  - commonly used to assess macular edema/holes/cysts, ARMD progression, epi-retinal membrane, retinal detachment (RD)
- **anterior segment optical coherence tomography (AS-OCT)**
  - non-invasive, cross-sectional, high-resolution imaging of cornea, aqueous, iris and lens
- **perimetry**
  - quantitative evaluation of visual fields, used to screen for scotomas and monitor progression (e.g. in glaucoma)
- **ultrasonography**
  - evaluation of orbit in real-time. A-scans (one-dimensional), B-scans (two-dimensional), and Doppler are all used (e.g. large RDs, foreign bodies, monitoring intraocular tumours)

## The Orbit

### Globe Displacement

Table 3. Exophthalmos (Proptosis) and Enophthalmos

	Exophthalmos (Proptosis)	Enophthalmos
<b>Definition</b>	<ul style="list-style-type: none"> <li>• Anterior displacement (protrusion) of the globe               <ul style="list-style-type: none"> <li>▪ Exophthalmos generally refers to an endocrine etiology or protrusion of &gt;18 mm (as measured by a Hertel exophthalmometer)</li> <li>▪ Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of &lt;18 mm</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Posterior displacement (retraction) of the globe</li> </ul>
<b>Investigations</b>	<ul style="list-style-type: none"> <li>• CT/MRI head/orbits, ultrasound orbits, thyroid function tests</li> </ul>	<ul style="list-style-type: none"> <li>• CT/MRI orbits</li> </ul>
<b>Etiology</b>	<ul style="list-style-type: none"> <li>• Note: rule out pseudoexophthalmos (e.g. lid retraction)</li> <li>• Graves' disease (unilateral or bilateral, most common cause in adults)</li> <li>• Orbital cellulitis (unilateral, most common cause in children)</li> <li>• 1° or 2° orbital tumours</li> <li>• Orbital/retrobulbar hemorrhage</li> <li>• Cavernous sinus thrombosis or fistula</li> </ul>	<ul style="list-style-type: none"> <li>• "Blow-out" fracture (see <i>Ocular Trauma</i>, OP42)</li> <li>• Orbital fat atrophy</li> <li>• Congenital abnormality</li> <li>• Metastatic disease</li> </ul>



### Preseptal Cellulitis

- infection of soft tissue anterior to orbital septum

#### Etiology

- usually follows periorbital trauma or dermal infection

#### Clinical Features (Table 4)

#### Treatment

- systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
  - e.g. amoxicillin-clavulanic acid
- if severe or child <1 yr, treat as orbital cellulitis

### Orbital Cellulitis

- **OCULAR and MEDICAL EMERGENCY**
- inflammation of orbital contents posterior to orbital septum
- common in children, elderly, and immunocompromised

#### Etiology

- usually 2° to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

#### Clinical Features (Table 4)

#### Treatment

- admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
- surgical drainage of abscess with close follow-up, especially in children



#### Periorbital and Orbital Cellulitis Before and After the Advent of Haemophilus influenzae type B Vaccination

*Ophthalmol* 2000;107:1450-1453  
**Study:** Retrospective case series.

**Patients:** 315 pediatric inpatients in Massachusetts with a discharge diagnosis of periorbital or orbital cellulitis.

**Results:** Prior to the introduction of the Hib vaccine, 11.7% of cases were culture positive for Hib. After the vaccination program was initiated, the case rate dropped to 3.5% ( $P=0.028$ ). All cases of orbital cellulitis were associated with sinusitis, and cases of periorbital cellulitis were most commonly associated with upper respiratory tract infections or sinusitis.



Orbital cellulitis is life-threatening if untreated (mortality of 17-20% without antibiotic use). Prompt diagnosis and treatment is essential.

### Complications

- optic nerve inflammation, cavernous sinus thrombosis, meningitis and brain abscess with possible loss of vision, death

**Table 4. Clinical Features of Preseptal and Orbital Cellulitis**

Finding	Preseptal Cellulitis	Orbital Cellulitis
Fever	May be present	Present
Lid edema	Moderate to severe	Severe
Conjunctival injection	Absent	Present
Chemosis	Absent or mild	Marked
Proptosis	Absent	Present
Pain on eye movement	Absent	Present
Ocular mobility	Normal	Decreased
Vision	Normal	Diminished $\pm$ diplopia
RAPD	Absent	May be seen
Leukocytosis	Moderate	Marked
ESR	Normal or elevated	Elevated
Additional findings	Skin infection	Sinusitis, dental abscess

## Lacrimal Apparatus

- tear film made up of three layers
  - outer oily layer (reduces evaporation): secreted by the Meibomian glands
  - middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  - inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
- tears drain from the eyes through the upper and lower lacrimal puncta  $\rightarrow$  superior and inferior canaliculi  $\rightarrow$  lacrimal sac  $\rightarrow$  nasolacrimal duct  $\rightarrow$  nasal cavity behind inferior concha (Figure 3)

## Dry Eye Syndrome (Keratoconjunctivitis Sicca)

### Etiology

- aqueous-deficient (lacrimal pathology)
  - Sjögren Syndrome (autoimmune etiology e.g. rheumatoid arthritis, SLE)
  - non-Sjögren Syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy, anticholinergics, antihistamines, diuretics,  $\beta$ -blockers)
- evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  - Meibomian gland dysfunction (posterior blepharitis)
  - vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  - eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  - preserved topical ocular medications
  - contact lenses, allergic conjunctivitis
- overlap of mixed etiologies common

### Clinical Features

- dry eyes, red eyes, foreign body sensation, blurred vision, tearing
- slit-lamp exam: decreased tear meniscus, decreased tear break up time (normally should be 10 s), SPK
- surface damage observed with fluorescein/Rose Bengal staining
- decreased distance in Schirmer's test

### Complications

- erosions and scarring of cornea

### Treatment

- medical: preservative-free artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used more than q1h PRN)
  - for severe cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) can be used
- procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
- treat underlying cause



Long term use of artificial tears with preservatives should be avoided when treating dry eyes.

## Epiphora (Excessive Tearing)

### Etiology

- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex (crocodile tears)

### Investigations

- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

### Treatment

- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy (see *Surgical Ophthalmology*, OP44) – forming a new connection between the lacrimal sac and the nasal cavity



Excessive tearing can be caused by dry eyes – if the tear quality is insufficient, “reflex tearing” may occur.

## Dacryocystitis

- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- commonly associated with *S. aureus*, *S. pneumoniae*, *Pseudomonas* species

### Clinical Features

- pain, swelling, redness over lacrimal sac at medial canthus
- epiphora, crusting,  $\pm$  fever
- digital pressure on the lacrimal sac may extrude pus through the punctum
- in the chronic form, epiphora may be the only symptom

### Treatment

- warm compresses, nasal decongestants, systemic and topical antibiotics
- if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy (see *Surgical Ophthalmology*, OP44)



## Dacryoadenitis

- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: *S. aureus*, mumps, EBV, herpes zoster, *N. gonorrhoeae*
- chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

### Clinical Features

- pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

### Treatment

- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder



## Lids and Lashes

### Lid Swelling

#### Etiology

- commonly due to allergy, with shriveling of skin between episodes
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatochalasis (loose skin due to aging or heredity)
- lid cellulitis, thyroid disease (e.g. myxedema), trauma, chemosis



## Ptosis

- drooping of upper eyelid

### Etiology

- aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
  - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- mechanical
  - incomplete opening of eyelid due to mass or scarring
- neuromuscular
  - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  - CN III palsy
  - Horner's syndrome (see *Constricted Pupil*, Horner's Syndrome, OP32)
- congenital
- pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)

### Treatment

- surgery

## Trichiasis

- eyelashes turned inwards
- may result from chronic inflammatory lid diseases (e.g. blepharitis), Stevens-Johnson syndrome, trauma, burns
- patient complains of red eye, foreign body sensation, tearing
- may result in corneal ulceration and scarring

### Treatment

- topical lubrication, eyelash plucking, electrolysis, cryotherapy

## Entropion

- lid margin turns in towards globe causing tearing, foreign body sensation, and red eye
- most commonly affects lower lid
- may cause abrasions with 2° corneal scarring

### Etiology

- involutional (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital

### Treatment

- lubricants, evert lid with tape, surgery



#### Testing for Entropion

Forced lid closure: Ask patient to tighten lid then open. In entropion, lid rolls inwards.

## Ectropion

- lid margin turns outward from globe causing tearing and possibly exposure keratitis

### Etiology

- involutional (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, surgery)
- mechanical (lid edema, tumour, herniated fat)
- congenital

### Treatment

- topical lubrication, surgery



#### Testing for Ectropion

Snapback test: Pull eyelid inferiorly. In ectropion, lid remains away from globe.

## Hordeolum (Stye)



- acute inflammation of eyelid gland: either Meibomian glands (internal lid) or glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)
- infectious agent is usually *S. aureus*
- painful, red swelling of lid

### Treatment

- warm compresses, lid care, gentle massage
- topical antibiotics (e.g. erythromycin ointment bid)
- usually resolves in 2-5 d

## Chalazion

- chronic granulomatous inflammation of Meibomian gland often preceded by an internal hordeolum
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, Meibomian gland carcinoma

### Treatment

- warm compresses
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy



#### Hordeolum vs. Chalazion

Hordeolums are due to an infectious etiology, whereas chalazions are granulomatous inflammation.

## Blepharitis

- inflammation of lid margins

### Etiology

- two main types
  - staphylococcal (*S. aureus*): ulcerative, dry scales
  - seborrheic: no ulcers, greasy scales

### Clinical Features

- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids ("toothpaste sign")

### Complications

- recurrent chalazia
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

### Treatment

- warm compresses and lid scrubs with diluted "baby shampoo"
- topical or systemic antibiotics as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids



## Xanthelasma

- eyelid xanthoma (lipid deposits in dermis of lids)
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (approximately 50% of patients)
- common in the elderly, more concerning in the young

### Treatment

- excision for cosmesis only, commonly recurs

## Conjunctiva

- thin, vascular mucous membrane/epithelium
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

## Pinguecula

- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea
- associated with sun and wind exposure, aging
- common, benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops



## Pterygium



- fibrovascular triangular encroachment of epithelial tissue onto the cornea, usually nasally
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (5%)

## Subconjunctival Hemorrhage



- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, hypertension
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- if recurrent, consider medical/hematologic work-up

## Conjunctivitis



### Etiology

- infectious
  - bacterial, viral, chlamydial, fungal, parasitic
- non-infectious
  - allergic: atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
  - 2° to another disorder: dacryocystitis, dacryoadenitis, cellulitis, Kawasaki's disease

### Clinical Features

- red eye (conjunctival injection often with limbal pallor), chemosis, subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, lid edema
- preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)



- Enlarged lymph nodes suggest infectious etiology, especially viral or chlamydial conjunctivitis
- Temporal conjunctival lymphatics drain to preauricular nodes, and nasal to submandibular nodes



- Follicles are usually seen in viral and chlamydial conjunctivitis
- Papillae are usually seen in allergic and bacterial conjunctivitis

## ALLERGIC CONJUNCTIVITIS

### Atopic

- associated with rhinitis, asthma, dermatitis, hay fever
- small papillae, chemosis, thickened and erythematous lids, corneal neovascularization
- seasonal (pollen, grasses, plant allergens)
- treatment: cool compresses, antihistamine, mast cell stabilizer (e.g. ketotifen, olopatadine)



### Types of Discharge

- Allergic: mucoid
- Viral: watery
- Bacterial: purulent
- Chlamydial: mucopurulent

### Giant Papillary Conjunctivitis

- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva
- treatment: clean, change or discontinue use of contact lens

### Vernal Conjunctivitis

- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 yr then resolves
- treatment: consider topical steroid, topical cyclosporine (by ophthalmologist)

## VIRAL CONJUNCTIVITIS



- serous discharge, lid edema, follicles
- subepithelial corneal infiltrates
- may be associated with rhinorrhea
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye
- mainly due to adenovirus – highly contagious for up to 12 d

### Treatment

- cool compresses, topical lubrication
- usually self-limiting (7-12 d)
- proper hygiene is very important

**BACTERIAL CONJUNCTIVITIS**

- purulent discharge, lid swelling, papillae, conjunctival injection, chemosis
- common agents include *S. aureus*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*
- in neonates or if sexually active must consider *N. gonorrhoeae* (invades cornea to cause keratitis)
- *Chlamydia trachomatis* is the most common cause in neonates (see *Chlamydial Conjunctivitis*, below)

**Treatment**

- topical broad-spectrum antibiotic
- systemic antibiotics if indicated, especially in neonates and children
- usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment

**CHLAMYDIAL CONJUNCTIVITIS**

- caused by *Chlamydia trachomatis*
- affects neonates (ophthalmia neonatorum) on day 3-5, sexually active individuals
- causes trachoma and inclusion conjunctivitis

**Trachoma**

- leading infectious cause of blindness in the world
- severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
- initially, follicles on superior palpebral conjunctiva
- treatment: topical and systemic tetracycline

**Inclusion Conjunctivitis**

- chronic conjunctivitis with follicles and subepithelial infiltrates
- most common cause of conjunctivitis in newborns
- prevention: topical erythromycin at birth
- treatment: topical and systemic tetracycline, doxycycline or erythromycin

**Antibiotics versus Placebo for Acute Bacterial Conjunctivitis**

Cochrane DB Syst Rev 2006;2:CD001211

**Study:** Cochrane systematic review and meta-analysis of 5 heterogeneous trials investigating the efficacy of topical antibiotic treatment for bacterial conjunctivitis.

**Patients:** 1034 participants randomized to topical antibiotic treatment or placebo.

**Results:** Topical antibiotics are beneficial in improving early (days 2 to 5) clinical and microbiological remission rates, with respective risk ratios (RR) of 1.24 and 1.77, respectively. Later (days 6 to 10) cure rates are lower than earlier values, with a clinical RR of 1.11 and a microbiological RR of 1.56. Most cases would, however, clinically resolve spontaneously on days 2-5 with placebo treatment only (65%). There were no reported serious outcomes in either group.

**Conclusion:** Topical antibiotic treatment of acute bacterial conjunctivitis is associated with a significantly improved rate of early clinical and microbiological remission, although most cases are self-limiting, and serious sight-threatening complications are rare.

## Sclera

- white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

## Episcleritis

- immunologically mediated inflammation of episclera
- 1/3 bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

**Etiology**

- mostly idiopathic
- in 1/3 of cases, associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, syphilis), inflammatory bowel disease, rosacea, atopy

**Clinical Features**

- usually asymptomatic; may have discomfort, heat sensation, red eye (often interpalpebral), rarely pain
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial conjunctival vessels)

**Treatment**

- generally self limited, recurrent in 2/3 of cases
- topical steroid for 3-5 d if painful (prescribed and monitored by ophthalmologist)



To differentiate between episcleritis and scleritis, place a drop of phenylephrine 2.5% (Mydrin®; AK-Dilate®) in the affected eye. Re-examine the vascular pattern 10-15 min later. Episcleral vessels should blanch. Scleral vessels should not.



## Scleritis

- usually bilateral: diffuse, nodular, or necrotizing
- anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing
- posterior scleritis: rapidly progressive blindness, may cause exudative RD
- more common in women and elderly

### Etiology

- may be a manifestation of systemic disease
- collagen vascular disease, e.g. SLE, rheumatoid arthritis, ankylosing spondylitis
- granulomatous, e.g. tuberculosis, sarcoidosis, syphilis
- metabolic, e.g. gout, thyrotoxicosis
- infectious, e.g. *S. aureus*, *S. pneumoniae*, *P. aeruginosa*, herpes zoster
- chemical or physical agents (e.g. thermal, alkali, or acid burns)
- idiopathic

### Clinical Features

- severe pain, photophobia, red eye, decreased vision
- pain is best indicator of disease progression
- inflammation of scleral, episcleral, and conjunctival vessels
- may have anterior chamber cells and flare, corneal infiltrate, scleral thinning
- sclera may have a blue hue (best seen in natural light), due to rearranged scleral fibres
- scleral edema or thinning
- failure to blanch with topical phenylephrine

### Treatment

- systemic NSAID or steroid (topical steroids are not effective)
- treat underlying etiology



#### Scleromalacia Perforans

- Asymptomatic anterior necrotizing scleritis without inflammation
- Strongly associated with rheumatoid arthritis
- May result in scleral thinning
- Traumatic perforation can easily occur – examine eye very gently

## Cornea

- function
  - transmission of light
  - refraction of light (2/3 of total refractive power of eye)
  - barrier against infection, foreign bodies
- transparency due to avascularity, uniform structure and deturgescence (relative dehydration)
- 5 layers (anterior to posterior): epithelium, Bowman's membrane, stroma, Descemet's membrane, endothelium (dehydrates the cornea; dysfunction leads to corneal edema)
- extensive sensory fibre network (V1 distribution); therefore abrasions and inflammation (keratitis) are very painful

## Foreign Body

- foreign material in or on cornea
- may have associated rust ring if metallic
- patients may note tearing, photophobia, foreign body sensation, red eye
- signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, anterior chamber cells/flare

### Complications

- abrasion, infection, scarring, rust ring, 2° iritis

### Treatment

- remove under magnification using local anesthetic and sterile needle or refer to ophthalmology (depending on depth and location)
- treat as per corneal abrasion



Foreign body behind lid may cause multiple vertical corneal epithelial abrasions due to blinking.



Topical analgesics should only be used to facilitate examination. They should NEVER be used as treatment for any ocular problem.



NEVER patch abrasion if patient wears contact lenses (prone to *Pseudomonas* infection).



Corneal abrasions from organic matter (e.g. twig, finger nail, etc.) have higher recurrence, even years later.

## Corneal Abrasion

- epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (Figure 14)

### Clinical Features (Table 5)

- pain, redness, tearing, photophobia, foreign body sensation
- de-epithelialized area stains with fluorescein dye
- pain relieved with topical anesthetic

### Complications

- infection, ulceration, recurrent erosion, 2° iritis

### Treatment

- topical antibiotic (drops or ointment)
- consider topical NSAID, cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch
- most abrasions clear spontaneously within 24-48 h

## Recurrent Erosions

- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

### Etiology

- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

### Treatment

- as for corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment at bedtime for 3 mo, topical lubrication
- bandage contact lens, anterior stromal puncture or phototherapeutic keratectomy for chronic recurrences

## Corneal Ulcer

### Etiology

- local necrosis of corneal tissue due to infection
- infection is usually bacterial, rarely viral, fungal or protozoan (*Acanthamoeba*)
- 2° to corneal exposure, abrasion, foreign body, contact lens use (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

### Clinical Features

- pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- may develop corneal edema, conjunctival injection, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

### Complications

- decreased vision, corneal perforation, iritis, endophthalmitis

### Investigations

- Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect penetrating lesions. Any aqueous leakage will change dark orange dye to bright yellow-green at site of wound

### Treatment

- urgent referral to ophthalmology
- culture prior to treatment
- topical antibiotics every hour
- must treat vigorously to avoid complications

**Table 5. Corneal Abrasion vs. Corneal Ulcer**

	Abrasion	Ulcer
<b>Time Course</b>	Acute (instantaneous)	Subacute (days)
<b>History of Trauma</b>	Yes	Not usually
<b>Cornea</b>	Clear	White, necrotic area
<b>Iris Detail</b>	Clear	Obscured
<b>Corneal Thickness</b>	Normal	May have crater defect/thinning
<b>Extent of Lesion</b>	Limited to epithelium	Extension into stroma

## Herpes Simplex Keratitis

- usually HSV type 1 (90% of population are carriers)
- may be triggered by stress, fever, sun exposure, immunosuppression

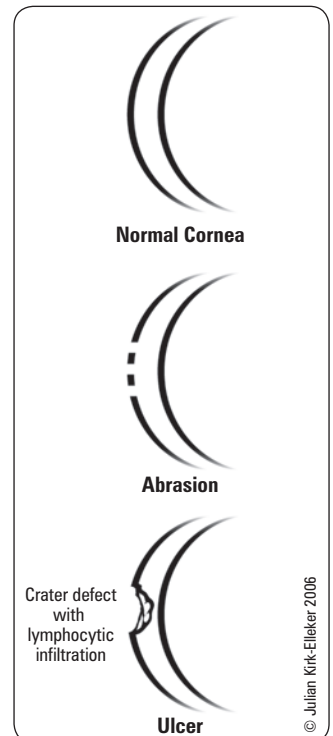
### Clinical Features

- pain, tearing, foreign body sensation, red eye, may have decreased vision, eyelid edema
- corneal hypoesthesia
- dendritic (thin and branching) lesion in epithelium that stains with fluorescein



### Corneal Abrasion: To Patch or Not to Patch

Patching for corneal abrasion. *Cochrane DB Syst Rev* 2006;2:CD004764  
Patching is not indicated for simple corneal abrasions, measuring less than 10 mm. There is no improvement in healing rates on days 1-3, no changes in reported pain and no difference in the use of antibiotics between the patch and non-patch groups.



**Figure 14. Corneal abrasion vs. ulcer**



### Abrasion vs. Ulcer on Slit Lamp

An abrasion appears clear while an ulcer is more opaque.



### Antiviral Treatment and other Therapeutic Interventions for Herpes Simplex Virus Epithelial Keratitis

*Cochrane DB Syst Rev* 2010;12:CD002898  
Rates of corneal re-epithelialization after acute HSV corneal epithelial keratitis are similar after treatment with trifluridine or acyclovir, and significantly better than after treatment with idoxuridine or vidarabine. Brivudine and ganciclovir are not inferior to acyclovir. Combining an antiviral agent with Interferon or corneal epithelial debridement did not improve outcomes overall, but did hasten corneal healing. Debridement with concomitant antiviral treatment was more effective than debridement alone.

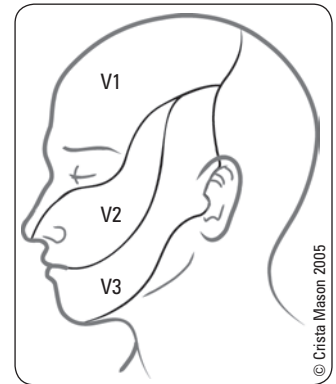


**Complications**

- corneal scarring (can lead to loss of vision)
- chronic interstitial keratitis due to penetration of virus into stroma
- 2° iritis, 2° glaucoma

**Treatment**

- topical antiviral such as trifluridine, consider systemic antiviral such as acyclovir
- dendritic debridement
- NO STEROIDS initially – may exacerbate condition
- ophthalmologist must exercise caution if adding topical steroids for chronic keratitis or iritis

**Figure 15. Trigeminal distribution****Herpes Zoster**

- dermatitis of the forehead (CN V1 territory) may involve globe
- Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then eye will be involved in approximately 75% of cases
- if no nasal involvement, eye is involved in 1/3 of patients

**Clinical Features**

- pain, tearing, photophobia, red eye
- corneal edema, pseudodendrite, superficial punctate keratitis
- corneal hypoesthesia

**Complications**

- corneal keratitis, ulceration, perforation and scarring
- 2° iritis, 2° glaucoma, cataract
- muscle palsies (rare) due to CNS involvement
- occasionally severe post-herpetic neuralgia

**Treatment**

- oral antiviral (acyclovir, valacyclovir, or famciclovir) immediately
- topical steroids, cycloplegia as indicated for keratitis, iritis
- erythromycin ointment if conjunctival involvement



Steroid treatment for ocular disorders should only be prescribed and supervised by an ophthalmologist, as they can impair corneal healing and exacerbate herpetic keratitis.

**Keratoconus**

- bilateral paracentral thinning and bulging (ectasia) of the cornea to form a conical shape
- usually sporadic, but associated with Down's syndrome, atopy, contact lens use (theorized to be related to chronic vigorous eye rubbing)
- associated with breaks in Descemet's and Bowman's membrane
- results in irregular astigmatism, scarring, stromal edema

**Treatment**

- attempt correction with spectacles or contact lens
- cross-linking treatment may halt or slow disease progression
- intrastromal corneal ring segments can help flatten the corneal cone
- penetrating keratoplasty (corneal transplant) 90% successful
- post-operative complications: endophthalmitis, graft rejection, graft failure, graft dehiscence



To detect keratoconus, look for bulging of the lower eyelid when the patient looks downward (Munson's sign).

**Arcus Senilis**

- hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
- common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
- may be associated with hypercholesterolemia if age <40 yr, check lipid profile
- no associated visual symptoms, no complications, no treatment necessary

**Kayser-Fleischer Ring**

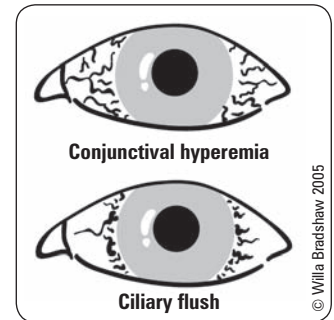
- brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
- due to deposition of copper pigment in Descemet's membrane
- associated with Wilson's disease
- no associated symptoms or complications of ring
- treat underlying disease

## The Uveal Tract

- uveal tract (from anterior to posterior)= iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina


## Uveitis

- uveal inflammation which may involve one or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, malignant causes
- should be managed by an optometrist or ophthalmologist
- anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis or panuveitis based on primary site of inflammation



**Figure 16. Conjunctival hyperemia vs. ciliary flush**

**Table 6. Anatomic Classification of Uveitis**

	Anterior Uveitis (Iritis)	Intermediate Uveitis	Posterior Uveitis
<b>Location</b>	<ul style="list-style-type: none"> <li>• Inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), both = iridocyclitis</li> <li>• Usually unilateral</li> </ul>	<ul style="list-style-type: none"> <li>• The vitreous is the major site of the inflammation</li> </ul>	<ul style="list-style-type: none"> <li>• Inflammation of the choroid and/or retina</li> </ul>
<b>Etiology</b> 	<ul style="list-style-type: none"> <li>• Usually idiopathic</li> <li>• Connective tissue diseases (see <a href="#">Rheumatology</a>, RH8) <ul style="list-style-type: none"> <li>▪ HLA-B27: reactive arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease</li> <li>▪ Non-HLA-B27: juvenile idiopathic arthritis</li> </ul> </li> <li>• Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster</li> <li>• Other: sarcoidosis, trauma, large abrasion, post ocular surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Mostly idiopathic, 2° causes include sarcoidosis, Lyme disease and multiple sclerosis</li> </ul>	<ul style="list-style-type: none"> <li>• Bacterial: syphilis, tuberculosis</li> <li>• Viral: herpes simplex virus, cytomegalovirus in AIDS</li> <li>• Fungal: histoplasmosis, candidiasis</li> <li>• Parasitic: toxoplasmosis (most common cause), toxocara</li> <li>• Immunosuppression may predispose to any of the above infections</li> <li>• Autoimmune: Behçet's disease (triad of oral ulcers, genital ulcers, and posterior uveitis)</li> <li>• Malignancies (masquerade syndrome): metastatic lesions, malignant melanoma</li> </ul>
<b>Clinical Features</b>	<ul style="list-style-type: none"> <li>• Photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased VA (in severe cases with hypopyon), lacrimation</li> <li>• Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle)</li> <li>• Anterior chamber "cells" (WBC in anterior chamber due to anterior segment inflammation) and "flare" (protein precipitates in anterior chamber 2° to inflammation), hypopyon (collection of neutrophilic exudates inferiorly in the anterior chamber)</li> <li>• Occasionally keratic precipitates (clumps of cells on corneal endothelium)</li> <li>• Iritis typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis, or iritis from herpes simplex and zoster may cause an inflammatory glaucoma (trabeculitis)</li> </ul>	<ul style="list-style-type: none"> <li>• Insidious onset of blurred vision, accompanied by vitreous floaters</li> <li>• Initial symptoms are usually unilateral but inflammatory changes are usually bilateral and asymmetric</li> <li>• Associated with anterior uveitis, most severe cases of 2° intermediate uveitis</li> <li>• Vitreous cells, condensations, and snowballs (vitreous aggregates of inflammatory cells)</li> <li>• Posterior segment 'snowbank' = grey-white fibrovascular plaque at the pars plana</li> </ul>	<ul style="list-style-type: none"> <li>• Painless as choroid has no sensory innervation</li> <li>• Often no conjunctival or scleral injection present</li> <li>• Decreased VA</li> <li>• Floaters (debris and inflammatory cells)</li> <li>• Vitreous cells and opacities</li> <li>• Hypopyon formation</li> </ul>
<b>Complications</b>	<ul style="list-style-type: none"> <li>• Inflammatory glaucoma</li> <li>• Posterior synechiae <ul style="list-style-type: none"> <li>▪ Adhesions of posterior iris to anterior lens capsule</li> <li>▪ Indicated by an irregularly shaped pupil</li> <li>▪ If occurs 360°, entraps aqueous in posterior chamber, iris bows forward "iris bombe" → angle closure glaucoma</li> </ul> </li> <li>• Peripheral anterior synechiae (rare): adhesions of iris to cornea → secondary angle closure glaucoma</li> <li>• Cataracts</li> <li>• Band keratopathy (with chronic iritis) <ul style="list-style-type: none"> <li>▪ Superficial corneal calcification keratopathy</li> </ul> </li> <li>• Macular edema with chronic iritis</li> </ul>	<ul style="list-style-type: none"> <li>• Cystoid macular edema (30% of cases), cataract, and glaucoma</li> </ul>	<ul style="list-style-type: none"> <li>• Macular edema</li> <li>• Vitritis</li> <li>• Neovascularization</li> <li>• Visual field loss/scotoma</li> </ul>
<b>Treatment</b>	<ul style="list-style-type: none"> <li>• Mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm</li> <li>• Steroids: topical, sub-tenon or systemic</li> <li>• Systemic analgesia</li> <li>• Extensive medical workup may be indicated to r/o 2° causes</li> </ul>	<ul style="list-style-type: none"> <li>• Systemic or sub-tenon/intravitreal steroids and immunosuppressive agents</li> <li>• Vitrectomy, cryotherapy or laser photocoagulation to the "snowbank"</li> </ul>	<ul style="list-style-type: none"> <li>• Steroids: sub-tenon, intravitreal or systemic if indicated (e.g. threat of vision loss)</li> </ul>

## Lens

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

## Cataracts

- any opacity of the lens, regardless of etiology
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, posterior subcapsular

### Etiology

- acquired
  - age-related (over 90% of all cataracts)
  - cataract associated with systemic disease (may have juvenile onset)
    - ♦ diabetes mellitus
    - ♦ metabolic disorders (e.g. Wilson's disease, galactosemia, homocystinuria)
    - ♦ hypocalcemia
  - traumatic (may be rosette shaped)
  - intraocular inflammation (e.g. uveitis)
  - toxic (steroids, phenothiazines)
  - radiation
- congenital
  - high myopia
  - present with altered red reflex or leukocoria
  - treat promptly to prevent amblyopia

### Clinical Features

- gradual, painless, progressive decrease in VA
- glare, dimness, halos around lights at night, monocular diplopia
- "second sight" phenomenon: patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
  - patient may read without previously needed reading glasses
- diagnose by slit-lamp exam, and by noting changes in red reflex using ophthalmoscope
- may impair view of retina during funduscopy

### Treatment

- medical: attempt correction of refractive error, no strong evidence suggesting benefit of vitamin supplementation
- surgical: definitive treatment
  - indications for surgery
    - ♦ to improve visual function in patients whose visual loss leads to functional impairment (no need to wait for "ripe" cataract, may postpone surgery as long as one eye has sufficient vision)
    - ♦ to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
    - ♦ congenital or traumatic cataracts
  - phacoemulsification (phaco = lens)
    - ♦ most commonly used surgical technique (see *Surgical Ophthalmology*, OP44)
  - post-operative complications
    - ♦ RD, endophthalmitis, dislocated IOL, macular edema, glaucoma
    - ♦ with new foldable IOLs that have truncated edges, <10% of patients get posterior capsular opacification, which should be treated with YAG laser

### Prognosis

- excellent if not complicated by other ocular disease

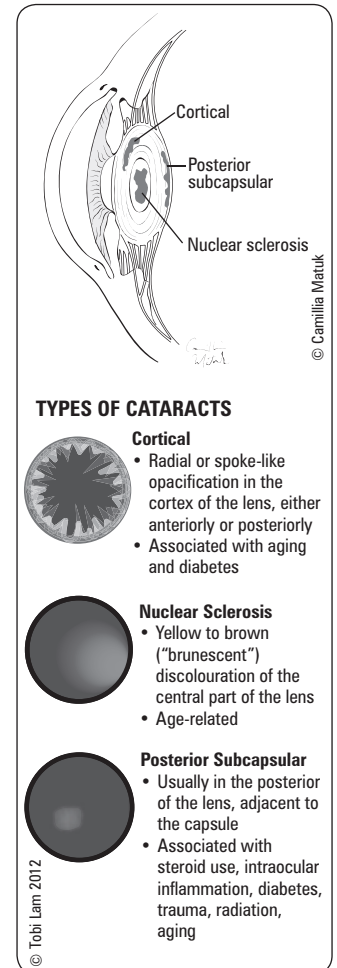


Figure 17. Types of cataracts

## Dislocated Lens (Ectopia Lentis)

### Etiology

- associated with Marfan's Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic



**Clinical Features**

- decreased VA
- may get unilateral diplopia
- iridodonesis (quivering of iris with movement)
- direct ophthalmoscopy may elicit abnormal red reflex

**Complications**

- cataract, glaucoma, uveitis

**Treatment**

- surgical correction  $\pm$  lens replacement

## Vitreous

- clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, pars plana, and along major retinal blood vessels

## Posterior Vitreous Detachment (PVD)

**Etiology**

- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, molecules that hold water condense causing vitreous floaters
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

**Clinical Features**

- floaters, flashes of light

**Complications**

- traction at areas of abnormal vitreoretinal adhesions may cause retinal tears/detachment
- retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
- complications more common in high myopes and following ocular trauma (blunt or perforating)

**Treatment**

- acute onset of PVD requires a dilated fundus exam to r/o retinal tears/detachment
- no specific treatment available for floaters/flashes of light



**Floaters:** "bugs", "cobwebs", or "spots" of vitreous condensation that change with eye position.



**Weiss' Ring:** formed by glial tissue around the optic disc that remains attached to the detached posterior vitreous.



Although most floaters are benign, new or markedly increased floaters or flashes of light require a dilated fundus exam to r/o retinal tears/detachment.

## Vitreous Hemorrhage

- bleeding into the vitreous cavity

**Etiology**

- proliferative diabetic retinopathy (PDR)
- retinal tear/detachment
- PVD
- retinal vein occlusion
- trauma

**Clinical Features**

- sudden loss of VA
- may be preceded by many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

**Treatment**

- ultrasound (B-scan) to r/o retinal detachment
- expectant: in non-urgent cases (e.g. no retinal detachment), blood usually resorbs in 3-6 mo
- surgical: vitrectomy  $\pm$  retinal detachment repair  $\pm$  retinal endolaser to possible bleeding sites/vessels



Any time a vitreous or retinal hemorrhage is seen in a child, must r/o child abuse.

## Endophthalmitis and Vitritis

- intraocular infection: acute, subacute, or chronic

### Etiology

- most commonly a postoperative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal

### Clinical Features

- painful, red eye, photophobia, discharge
- severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased IOP, etc.)

### Treatment (see *Ocular Trauma*, OP42)

- **OCULAR EMERGENCY:** presenting vision best indicates prognosis
- LP or worse: admission, immediate vitrectomy and intravitreal antibiotics to prevent loss of vision
- HM or better: vitreous tap for culture and intravitreal antibiotics
- topical fortified antibiotics



Remember to inquire about tetanus status in post-traumatic endophthalmitis.



**Endophthalmitis Vitrectomy Study**  
Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study. *Arch Ophthalmol* 1995;113:1479-1496  
For treatment of post-cataract surgery endophthalmitis:  
• Intravitreal antibiotics preferred over systemic antibiotics  
• Vitrectomy indicated only if vision LP or worse

## Retina

- composed of two parts (Figure 2)
  - neurosensory retina: comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
  - retinal pigmented epithelium (RPE) layer: external to neurosensory retina
- macula: rich in cones (for colour vision); most sensitive area of retina; looks darker due to lack of retinal vessels and thinning of retina in this region; 15° temporal and slightly below the optic disc
- fovea: centre of macula; responsible for acute, fine vision
- optic disc: slightly oval vertically, pinkish colour with centrally depressed yellow cup (normal cup:disc ratio is <0.5), retinal artery and vein pass through cup
- ora serrata: irregularly-shaped, anterior margin of the retina (can only be visualized with indirect ophthalmoscopy of the far peripheral retina, or through a Goldmann 3 mirror lens)

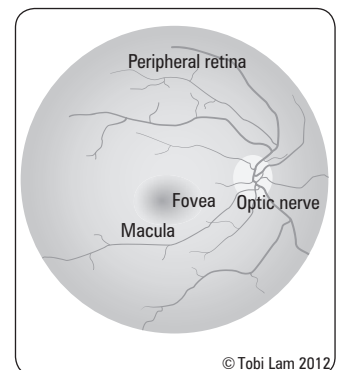


Figure 18. Retina

## Central Retinal Artery Occlusion (CRAO)

### Etiology

- emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
- thrombus
- temporal arteritis

### Clinical Features

- sudden, painless (except in GCA), severe monocular loss of vision
- RAPD
- patient may have experienced transient episodes in the past (amaurosis fugax)
- fundoscopy
  - "cherry-red spot"
  - retinal pallor
  - narrowed arterioles, boxcarring (segmentation of blood in arteries)
  - cotton-wool spots (retinal infarcts)
  - cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations
  - after ~6 wk cherry-red spot recedes and optic disc pallor becomes evident

### Treatment

- **OCULAR EMERGENCY:** attempt to restore blood flow within 2 h
- the sooner the treatment = better prognosis (irreversible retinal damage if >90 min of complete CRAO)
  - massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
  - decrease intraocular pressure
    - ♦ topical  $\beta$ -blockers
    - ♦ inhaled oxygen-carbon dioxide mixture
    - ♦ IV acetazolamide
    - ♦ IV mannitol (draws fluid from eye)
    - ♦ drain aqueous fluid – anterior chamber paracentesis (carries risk of endophthalmitis)
  - treat underlying cause to prevent CRAO in other eye



**Hallmark of CRAO**  
"Cherry-red spot" located at centre of macula (visualisation of unaffected highly vascular choroid through the thin fovea).



Treatment for a central retinal artery occlusion (CRAO) must be initiated within 2 h of symptom onset for any hope of restoring vision.

## Branch Retinal Artery Occlusion (BRAO)

- only part of the retina becomes ischemic resulting in a visual field loss
- more likely to be of embolic etiology than CRAO; need to search for source
- management: ocular massage to dislodge embolus if VA is affected

## Central/Branch Retinal Vein Occlusion (CRVO/BRVO)

- second most frequent “vascular” retinal disorder after DR
- usually a manifestation of a systemic disease (e.g. hypertension, diabetes mellitus)
- thrombus occurs within the lumen of the blood vessel

### Predisposing Factors

- arteriosclerotic vascular disease
- hypertension
- diabetes mellitus
- glaucoma
- hyperviscosity (e.g. polycythemia rubra vera, sickle-cell disease, lymphoma, leukemia)
- drugs (e.g. oral contraceptive pill, diuretics)

### Clinical Features

- painless, monocular, gradual or sudden visual loss
- $\pm$  RAPD
- fundoscopy
  - “blood and thunder” appearance
  - diffuse retinal hemorrhages, cotton-wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - ♦ no RAPD, VA approximately 20/80
    - ♦ mild hemorrhage, few cotton wool spots
    - ♦ resolves spontaneously over weeks to months
    - ♦ may regain normal vision if macula intact
  - hemorrhagic/ischemic retinopathy
    - ♦ usually older patient with deficient arterial supply
    - ♦ RAPD, VA approximately 20/200, reduced peripheral vision
    - ♦ more hemorrhages, cotton wool spots, congestion
    - ♦ poor visual prognosis

### Complications

- degeneration of retinal pigment epithelium
- neovascularization of retina and iris (2° rubeosis), leading to 2° glaucoma
- vitreous hemorrhage
- macular edema

### Treatment

- no treatment available to restore vision in CRVO/BRVO
- treat underlying cause/contributing factor
- fluorescein angiography to determine extent of retinal non-perfusion (risk of neovascularization)
- retinal laser photocoagulation, or intravitreal anti-VEGF injection to reduce retinal or iris neovascularization and prevent neovascular glaucoma
- macular grid laser photocoagulation for the treatment of macular edema in BRVO, not CRVO, intravitreal or slow-release biodegradable corticosteroid, or anti-VEGF injection is effective in the treatment of macular edema in both CRVO and BRVO



#### Branch Vein Occlusion Study (BVOS)

Branch Vein Occlusion Study Group: Argon laser photocoagulation for macular edema in branch vein occlusion. *Am J Ophthalmol* 1984;98:271-282  
BVOS showed that argon laser treatment improves sight significantly in patients with macular edema following BRVO. The treatment also decreases the risk of vitreous hemorrhage.



The “blood and thunder” appearance on fundoscopy is very characteristic of a CRVO.



There is an 8-10% risk of developing CRVO or BRVO in other eye.



#### GENEVA phase 3 Trials In BRVO and CRVO

*Ophthalmology* 2010;117:1134-1146  
Randomized sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion.  
Dexamethasone intravitreal implant reduces the risk of vision loss and improves the speed and incidence of visual improvement in eyes with macular edema 2° to BRVO and CRVO.



Superotemporal retina is the most common site for horseshoe tears.

## Retinal Detachment (RD)

- cleavage in the plane between the neurosensory retina and the retinal pigment epithelium (RPE)
- three types
  - rhegmatogenous (most common)
    - ♦ caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - ♦ tears may be caused by posterior vitreous detachment (PVD), degenerative retinal changes, trauma or iatrogenically
    - ♦ incidence increases with advancing age, in high myopes and after ocular surgery/trauma
  - tractional
    - ♦ caused by traction (due to vitreal, epiretinal, or subretinal membrane) pulling the neurosensory retina away from the underlying RPE
    - ♦ found in conditions such as DR, CRVO, sickle cell disease, ROP, and ocular trauma
  - exudative
    - ♦ caused by damage to the RPE resulting in fluid accumulation in the subretinal space
    - ♦ main causes are intraocular tumours, posterior uveitis, central serous retinopathy



### Clinical Features

- sudden onset
- flashes of light
  - due to mechanical stimulation of the retinal photoreceptors
- floaters
  - hazy spots in the line of vision which move with eye position, due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/peripheral field loss
  - darkness in one field of vision when the retina detaches in that area
- loss of central vision (if macula “off”)
- decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
- ophthalmoscopy: detached retina is grey-white with surface blood vessels, loss of red reflex
- $\pm$  RAPD

### Treatment

- prophylactic: symptomatic tear (flashes or floaters) can be sealed off with laser/cryotherapy, with the goal of preventing progression to detachment
- therapeutic
  - rhegmatogenous
    - ♦ scleral buckle procedure (see *Surgical Ophthalmology*, OP44)
    - ♦ pneumatic retinopexy (see *Surgical Ophthalmology*, OP44)
    - ♦ both treatments above are used in combination with localization of retinal tears/holes and subsequent treatment with cryotherapy or laser to create adhesions between the RPE and the neurosensory retina
    - ♦ vitrectomy plus injection of gas or silicone oil in cases of recurrent detachment
  - tractional
    - ♦ vitrectomy  $\pm$  membrane removal/scleral buckling/injection of intraocular gas or silicone oil as necessary
  - exudative
    - ♦ treat underlying cause

### Complications

- loss of vision, vitreous hemorrhage, recurrent retinal detachment
- a retinal detachment is an emergency, especially if the macula is still attached (macula “on”)
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

## Retinitis Pigmentosa

- worldwide incidence between 1/3500 and 1/7000 people
- many forms of inheritance, most commonly autosomal recessive (60%)
- hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy

### Clinical Features

- night blindness, decreased peripheral vision (“tunnel vision”), decreased central vision (macular changes), glare (from cataract)

### Investigations

- fundoscopy: areas of “bone-spicule” pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
- electrophysiological tests: electroretinography (ERG) and electrooculography (EOG) assist in diagnosis

### Treatment

- no treatments available to reverse the condition; cataract extraction improves visual function; vitamin A and vitamin E supplementation can reduce progression of disease in some patients

## Leber’s Congenital Amaurosis

- worldwide incidence 1/80,000
- inherited degeneration, autosomal recessive
- symptoms: resting nystagmus, sluggish or no papillary response, severe vision loss/blindness
- diagnosis: 11 types, confirmed by genetic testing
- management: no treatments available to reverse the conditions for most forms; one form (LCA2) shown to be successfully treatable by gene replacement using adeno-associated virus



#### Berson et al. A Randomized Trial of Vitamin A and Vitamin E Supplementation for Retinitis Pigmentosa

*Arch Ophthalmol* 1993;111:761-772

**Objective:** To determine if vitamin A and/or vitamin E supplementations influence the progression of retinitis pigmentosa.

**Methods:** Randomized, controlled, double-blind trial. Eligible patients 18-49 yr of age ( $n = 601$ ) were assigned to one of four intervention groups: 15 000 IU/d of vitamin A and 3 IU/d vitamin E, 15 000 IU/d of vitamin A and 400 IU/d of vitamin E, 75 IU/d of vitamin A and 3 IU/d of vitamin E (trace vitamins), or 75 IU/d of vitamin A and 400 IU/d of vitamin E. Cone electroretinogram amplitude was the outcome measure. A subset of patients was identified to have higher initial cone electroretinogram amplitude ( $n = 354$ ). Patients were followed-up for a mean duration of 5.2 yr.

**Results:** Groups that received 15 000 IU/d of vitamin A had slower decline of retinal function compared to those who did not receive vitamin A ( $p = 0.01$ ). Among patients with higher initial cone electroretinogram amplitude, groups receiving 15 000 IU/d of vitamin A were less likely to have a decline in amplitude of  $\geq 50\%$  from baseline than those who did not ( $p = 0.01$ ). Groups receiving 400 IU/d of vitamin E were more likely to have a decline in amplitude than those who did not ( $p = 0.03$ ). **Conclusion:** Daily 15 000 IU supplementation of vitamin A may protect against retinal function decline while daily 400 IU supplementation of vitamin E may exacerbate retinal function decline among patients with retinitis pigmentosa.



#### Triad of Retinitis Pigmentosa

##### APO

Arteriolar narrowing  
Perivascular bony-spicule pigmentation  
Optic disc pallor



#### Retinitis Pigmentosa Inherited Forms

- Autosomal recessive: most common
- Autosomal dominant: best prognosis
- X-linked: worst prognosis



#### Age-dependent Effects of Gene Therapy for Leber’s Congenital Amaurosis: A Phase 1 Dose-escalation Trial

*Lancet* 2009;374:1597-605

**Objective:** To evaluate the effect of gene therapy on retinal and visual function among patients with Leber’s congenital amaurosis.

**Methods:** Phase 1 trial. Patients aged 8-44 ( $n = 12$ ) with RPE65-associated Leber’s congenital amaurosis received a single subretinal injection of adeno-associated virus (AAV) containing the gene encoding the protein needed for isomerohydrolase activity of the retinal pigment epithelium (RPE65) (AAV2-hRPE65v2) in the worst eye at low, medium, or high dose. Patients were assessed before and after injections. Outcomes were subjective and objective measures of vision.

**Results:** AAV2-hRPE65v2 was tolerated. No serious adverse events were recorded. Visual improvement was noted for all patients. All patients reported improved vision in dimly lit environments. Visual fields improved in all patients. Pupillary light responses were increased by at least 2 log unit for all patients. Greatest visual improvement was noted in children.

**Conclusion:** AAV2-hRPE65v2 is safe and improves vision among patients with Leber’s congenital amaurosis.

## Age-Related Macular Degeneration (ARMD)

- leading cause of irreversible blindness in the western world, associated with increasing age, usually bilateral
- 10% of people >65 yr old have some degree of ARMD
- female > male
- degenerative changes are concentrated at the macula, thus only central vision is lost; peripheral vision (important for navigation) is maintained so patients can usually maintain an independent lifestyle

### Classification

- **Non-Exudative/“Dry” (Non-Neovascular) ARMD**
  - most common type of ARMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow-white deposits between the retinal pigment epithelium (RPE) and Bruch's membrane (area separating inner choroidal vessels from RPE)
  - RPE atrophy: coalescence of depigmented RPE, clumps of focal hyperpigmentation or hypopigmentation
  - may progress to neovascular ARMD
- **Exudative/“Wet” (Neovascular) ARMD**
  - 10% of ARMD, but 80% of ARMD that results in severe visual loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch's membrane causing subsequent growth and proliferation of choroidal capillaries
  - may lead to serous detachment of overlying RPE and retina, hemorrhage and lipid precipitates into subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of hemorrhagic retinal detachment
  - leads to disciform scarring and severe central visual loss

### Risk Factors

- female
- increased age
- family history
- smoking
- Caucasian race
- blue irides

### Clinical Features

- variable degree of progressive central visual loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

### Investigations

- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography: assess degree of neovascularization – pathologic new vessels leak dye

### Treatment

- non-neovascular “dry” ARMD
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed-circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visors
  - see Age-related Eye Disease Study (AREDS) sidebar
- neovascular “wet” ARMD
  - see *Common Medications*, OP44
  - laser photocoagulation for neovascularization
  - 50% of choroidal neovascularization cannot be treated initially
  - no definitive treatment for disciform scarring
  - PDT with verteporfin (Visudyne®)
    - ♦ IV injection of verteporfin followed by low intensity laser to area of choroidal neovascularization
  - intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF)
    - ♦ pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®) (see OP45)



#### Age-related Eye Disease Study (AREDS)

The Age-Related Eye Disease Research Group:  
A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, β-carotene, and zinc for age-related macular degeneration and vision loss. AREDS Report No. 8. *Arch Ophthalmol* 2001;119:1417-1436  
AREDS studied the effect of high-dose combination of vitamin C, vitamin E, β-carotene, and zinc in patients with and without ARMD. Those who are already affected by ARMD showed 19% decrease in risk of further visual loss, whereas high dose supplementation showed no benefit in patients with early or no ARMD.



#### Wet ARMD Lesions on Fluorescein Angiography

Classic: well-defined leakage  
Occult: mottled or ill-defined leakage



#### Drusen vs. Exudate

Drusen: hyaline material secreted by RPE seen frequently in ARMD typically in peri-macular region  
Hard/Soft Exudates: lipid deposits in the retina associated with diabetic retinopathy and hypertension



#### Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

CATT Research Group. *NEJM* 2011;364:1897-1908  
**Study:** A multicentre, single-blind, randomized control trial comparing the effects of ranibizumab and bevacizumab on visual acuity in patients with age-related macular degeneration (ARMD).  
**Patients:** 1208 patients aged 50 or more with previously untreated ARMD and visual acuity between 20/25 and 20/320.  
**Intervention:** Intravitreal injections of ranibizumab vs. intravitreal injections of bevacizumab.  
**Results:** The monthly use of either bevacizumab or ranibizumab results in the same visual acuity outcome. This finding holds true for the mean visual acuity and the proportion of patients who gain 15 letters, lose 15 letters, or remain stable. Equivalent visual-acuity outcomes were observed with both the monthly and the as-needed regimens of ranibizumab.  
**Conclusion:** This study supports the use of either bevacizumab or ranibizumab for the treatment of neovascular ARMD. The continued global use of intravitreal bevacizumab is an equally effective, low-cost alternative to ranibizumab.

# Glaucoma



## Definition

- progressive optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

## Background

- aqueous is produced by the ciliary body and flows from the posterior chamber to the anterior chamber through the pupil, and drains into the episcleral veins via the trabecular meshwork and the Canal of Schlemm (Figure 20)
- an isolated increase in IOP is termed ocular hypertension (or glaucoma suspect) and these patients should be followed for increased risk of developing glaucoma (10% if IOP 20-30 mmHg; 40% if IOP 30-40 mmHg; and most if IOP >40 mmHg)
- pressures >21 mmHg are more likely to be associated with glaucoma; however, up to 50% of patients with glaucoma do not have IOP >21 mmHg
- loss of peripheral vision most commonly precedes central loss
- sequence of events: gradual pressure rise → increased C:D ratio → visual field loss

## Investigations

- medical and family history
- VA testing
- slit lamp exam to assess anterior chamber depth
- ophthalmoscopy to assess the disc features
- tonometry by applanation or indentation to measure IOP
- visual field testing
- pachymetry to measure corneal thickness
- future follow-up includes optic disc examination, IOP measurement, and visual field testing to monitor course of disease



### Anti-angiogenic Therapy with Anti-vascular Endothelial Growth Factor Modalities for Neovascular Age-related Macular Degeneration

*Cochrane DB Syst Rev* 2008;2:CD005139

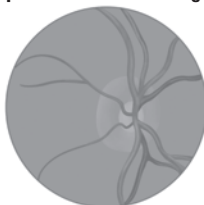
**Study:** Cochrane systematic review of RCTs investigating the use of anti-VEGF (vascular endothelial growth factor) modalities for the treatment of wet age-related macular degeneration (AMD).

**Patients:** Classic or occult wet type AMD.  
**Interventions:** Pegaptanib/Macugen® (aptamer comprised of ribonucleic acids that bind VEGF), ranibizumab/Lucentis® (anti VEGF fragment antibody) and verteporfin/Visudyne® photodynamic therapy (PDT).

**Results:** The MARINA trial showed that the pooled relative risk (RR) for a gain of 15 or more letters of visual acuity was 5.81 for ranibizumab versus placebo, while the FOCUS trial showed that the pooled RR for a gain of 15 or more letters at one year was 4.44 for a combination of ranibizumab + verteporfin PDT versus verteporfin PDT alone.

**Conclusion:** Ranibizumab offers significant benefit for the treatment of wet AMD with significant improvements in best corrected visual acuity at one year.

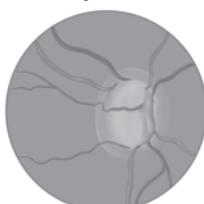
### Optic nerve head damage



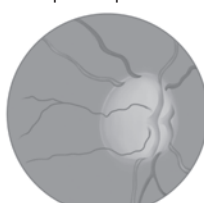
Pallor and cupping of optic disc (C:D ratio 0.2-0.3)



Concentric enlargement (C:D ratio 0.5)

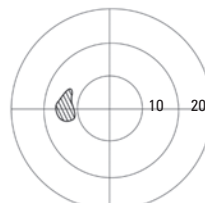


Superior expansion

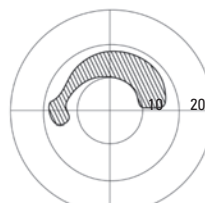


Advanced/total cupping

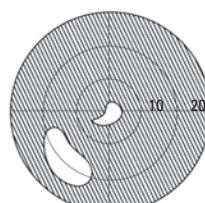
### Visual field changes



Small paracentral scotoma

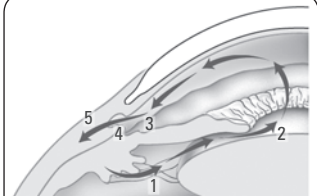


Arcuate defect



Temporal central island

© Diana Dai 2005



1. Ciliary body processes
2. Pupillary block
3. Pretrabecular
4. Trabecular and Canal of Schlemm
5. Post-trabecular

© Janice Wong

**Figure 20. Aqueous flow and sites of potential resistance**

**Figure 19. Glaucomatous damage**

## Primary Open Angle Glaucoma (POAG)

- most common form, >95% of all glaucoma cases
- due to obstruction of aqueous drainage within the trabecular meshwork and its drainage into the Canal of Schlemm
- insidious and asymptomatic, screening is critical for early detection

### Major Risk Factors

- elevated intraocular pressure (>21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic

### Minor Risk Factors

- myopia
- hypertension
- diabetes
- hyperthyroidism (Graves' disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 wk of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

### Clinical Features

- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased C:D ratio (vertical C:D >0.6)
  - significant C:D asymmetry between eyes (>0.2 difference)
  - thinning, notching of the neuroretinal rim
  - flame shaped disc hemorrhage
  - 360° of peripapillary atrophy
  - nerve fibre layer defect
  - large vessels become nasally displaced
- visual field loss
  - slow, progressive, irreversible loss of peripheral vision
  - paracentral defects, arcuate scotoma and nasal step are characteristics (Figure 19)
  - late loss of central vision if untreated

### Treatment

- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see *Glaucoma Medications*, Table 12, OP45)
  - increase aqueous outflow
    - ♦ topical cholinergics
    - ♦ topical prostaglandin analogues
    - ♦ topical  $\alpha$ -adrenergics
  - decrease aqueous production
    - ♦ topical  $\beta$ -blockers
    - ♦ topical and oral carbonic anhydrase inhibitor
    - ♦ topical  $\alpha$ -adrenergics
- laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
- trabeculectomy (see *Surgical Ophthalmology*, OP44)
- serial optic nerve head examinations, IOP measurements, and visual field testing to monitor disease course

## Normal Tension Glaucoma

- POAG with IOP in normal range
- often found in women >60 but may occur earlier
- damage to optic nerve may be due to vascular insufficiency

### Treatment

- treat reversible causes



Average IOP =  $15 \pm 3$  mmHg  
 Normal cup:disc  $\leq 0.4$   
 Suspect glaucoma if C:D ratio >0.6, C:D ratio between eyes >0.2, or cup approaches disc margin



### Open- and Closed-Angle Glaucoma

POAG	PACG
<ul style="list-style-type: none"> <li>• Common (95%)</li> <li>• Chronic course</li> <li>• Painless eye without redness</li> <li>• Moderately <math>\uparrow</math> IOP</li> <li>• Normal cornea and pupil</li> <li>• No N/V</li> <li>• No halos around light</li> </ul>	<ul style="list-style-type: none"> <li>• Rare (5%)</li> <li>• Acute onset</li> <li>• Painful red eye</li> <li>• Extremely <math>\uparrow</math> IOP</li> <li>• Hazy cornea</li> <li>• Mid-dilated pupil unreactive to light</li> <li>• <math>\pm</math> N/V, abdominal pain</li> <li>• Halos around light</li> </ul>



### Risk Factors for POAG

#### A FIAT

Age  
 Family History  
 IOP  
 African descent  
 Thin Cornea



### Reduction of Intraocular Pressure and Glaucoma Progression

*Arch Ophthalmol* 2002;120:1268-1279

**Study:** Randomized controlled clinical trial.

**Patients:** 255 participants, mainly selected through a population screening protocol, aged 50-80 with newly detected open-angle glaucoma, visual field defects, and a median intraocular pressure (IOP) of 20 mmHg.

**Intervention:** Participants were randomized to either topical  $\beta$ -blocker (betaxolol) plus argon, laser trabeculoplasty, or no initial treatment, with close observation for both groups. Median follow-up was 6 yr.

**Main Outcome:** Glaucoma progression as defined by visual field and optic disc abnormalities.

**Results:** IOP was reduced by 25% (mean 5.1 mmHg) in the treatment group. Glaucoma progression was evident in 62% of individuals in the control group vs. only 45% in the treatment group ( $p=0.007$ ). The progression was significantly later in the treatment group vs. the controls.



### The Ocular Hypertension Treatment Study

*Arch Ophthalmol-Chic* 2002;120:701-713

**Study:** Randomized clinical trial.

**Patients:** 1636 patients with no evidence of glaucomatous damage, aged 40 to 80 yr, and with intraocular pressure (IOP) between 24-32 mmHg in one eye and between 21-32 mmHg in the other eye.

**Intervention:** Randomized to observation or treatment with commercially available topical ocular hypotensive medication.

**Main Outcome:** Development of visual field abnormality or optic disc deterioration attributed to primary open-angle glaucoma (POAG).

**Results:** Mean reduction in IOP in the medication group was  $22.5\% \pm 9.9\%$  versus  $4.0\% \pm 11.6\%$  in the observation group. At 5 yr the probability of developing POAG was 4.4% in the medication group and 9.5% in the observation group ( $p<0.0001$ ).

**Conclusions:** Topical ocular hypotensive medication was effective in delaying or preventing the onset of POAG in individuals with elevated IOP.

## Secondary Open Angle Glaucoma

- increased IOP 2° to ocular/systemic disorders that obstruct the trabecular meshwork
  - steroid-induced glaucoma
  - traumatic glaucoma
  - pigmentary dispersion syndrome
  - pseudoexfoliation syndrome

## Primary Angle-Closure Glaucoma

- 5% of all glaucoma cases
- peripheral iris bows forward in an already susceptible eye with a shallow anterior chamber obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block, and results in inability of the aqueous to flow from the posterior chamber to the anterior chamber resulting in a sudden rise in IOP

### Risk Factors

- hyperopia: small eye, big lens – large lens crowds the angle
- age >70
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

### Clinical Features

- red, painful eye = **RED FLAG**
- unilateral, but other eye increased risk
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- corneal edema with conjunctival injection
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

### Complications

- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae, resulting in permanent angle closure

### Treatment

- refer to ophthalmologist – acute angle closure glaucoma is an **EMERGENCY**
  - laser iridotomy
  - aqueous suppressants and hyperosmotic agents
- medical treatment (see *Glaucoma Medications*, Table 12, OP45)
  - miotic drops (pilocarpine) to reverse pupillary block
  - decrease IOP
    - topical  $\beta$ -blockers
    - topical adrenergics
    - topical cholinergics
      - pilocarpine 1-4% q15min, up to q5min
    - systemic carbonic anhydrase inhibitors
      - IV acetazolamide 250-500 mg
    - systemic hyperosmotic agents
      - oral glycerine 1 g/kg
      - IV mannitol 1 g/kg

## Secondary Angle-Closure Glaucoma

### Uveitis

- inflamed iris adheres to lens (posterior synechiae)

### Neovascular Glaucoma

- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with proliferative diabetic retinopathy or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris vessels



#### Rule of Fours

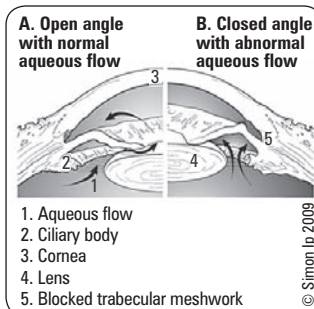
1/4 of general population using topical steroid for 4 wk, 4 x/d will develop an increase in IOP.



#### Collaborative Normal Tension Glaucoma Study

*Curr Opin Ophthalmol* 2003;14:86-90

Treatment aimed at lowering IOP by 30% in patients with normal tension glaucoma tends to reduce the rate of visual field loss. Due to variability in disease progression and a significant group that shows no visual field loss at 5 yr despite no treatment, further studies are needed to delineate which subgroups may benefit most from treatment.



**Figure 21. Normal open angle vs. angle-closure glaucoma**



#### Angle Closure Glaucoma

##### BACH

Tx with miotics and  $\beta$ -Blockers

Adrenergics

Cholinergics

Hyperosmotic agents



#### Medical Interventions for Primary Open Angle Glaucoma and Ocular Hypertension

*Cochrane DB Syst Rev* 2007;4:CD003167

**Study:** Cochrane systematic review of 26 trials and meta-analysis of 10 trials investigating the effectiveness of topical pharmacological therapies for primary open angle glaucoma (POAG) or ocular hypertension (OHT).

**Patients:** 4979 participants randomized in 26 trials. Patients had OHT with intraocular pressure (IOP) >21 mmHg or open angle glaucoma.

**Intervention:** Topical eye medications, including  $\beta$ -blockers, dorzolamide, brimonidine, pilocarpine and epinephrine versus each other and placebo.

**Main outcome:** Reduction of progression or prevention of onset of visual field defects.

**Results:** Meta-analysis on all trials that tested drugs against placebo or untreated controls demonstrated that lowering IOP reduces incidence of glaucomatous visual field defects, with an odds ratio of 0.62 (95% CI 0.47-0.81). However, this result is of limited practical use since different therapies were pooled. No single drug demonstrated significant visual field protection. However, as a class,  $\beta$ -blockers showed borderline significance in reducing onset of glaucoma in patients with OHT when compared to placebo, with an OR of 0.67 (95% CI 0.45-1.00).

**Conclusion:** Lowering IOP can reduce progression of visual field defects in patients with OHT.



## Pupils

- pupil size is determined by the balance between the sphincter muscle and the dilator muscle
- sphincter muscle is innervated by the parasympathetic nervous system
  - carried by CN III: pre- and post-ganglionic fibres synapse in ciliary ganglion, and use acetylcholine as the neurotransmitter
- dilator muscle is innervated by the sympathetic nervous system (SNS)
  - first order neuron = hypothalamus → brainstem → spinal cord
  - second order/preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
  - third order/postganglionic fibres originate in the superior cervical ganglion, neurotransmitter is noradrenaline
    - ♦ as a diagnostic test, 4-10% cocaine prevents the re-uptake of noradrenaline, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner's Syndrome)
  - see Figure 8 in [Neurology](#), N6



### 5 Targets of Retinal Signals

- Pre-tectal nucleus (pupillary reflex/eye movements)
- Lateral geniculate body of thalamus
- Superior colliculus (eye movements)
- Suprachiasmatic nucleus (optokinetic)
- Accessory optic system (circadian rhythm)



## Pupillary Light Reflex

- light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → bilateral midbrain
- impulses enter bilaterally in midbrain via pretectal area and Edinger-Westphal nuclei
- nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes

## Pupil Abnormalities



### Denervation Hypersensitivity

- when post-ganglionic fibres are damaged, the understimulated end-organ develops an excess of neuroreceptors and becomes hypersensitive
- postganglionic parasympathetic lesions (i.e. Adie's pupil)
  - pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
- postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner's syndrome)
  - pupil will dilate with 0.125% adrenaline, normal pupil will not

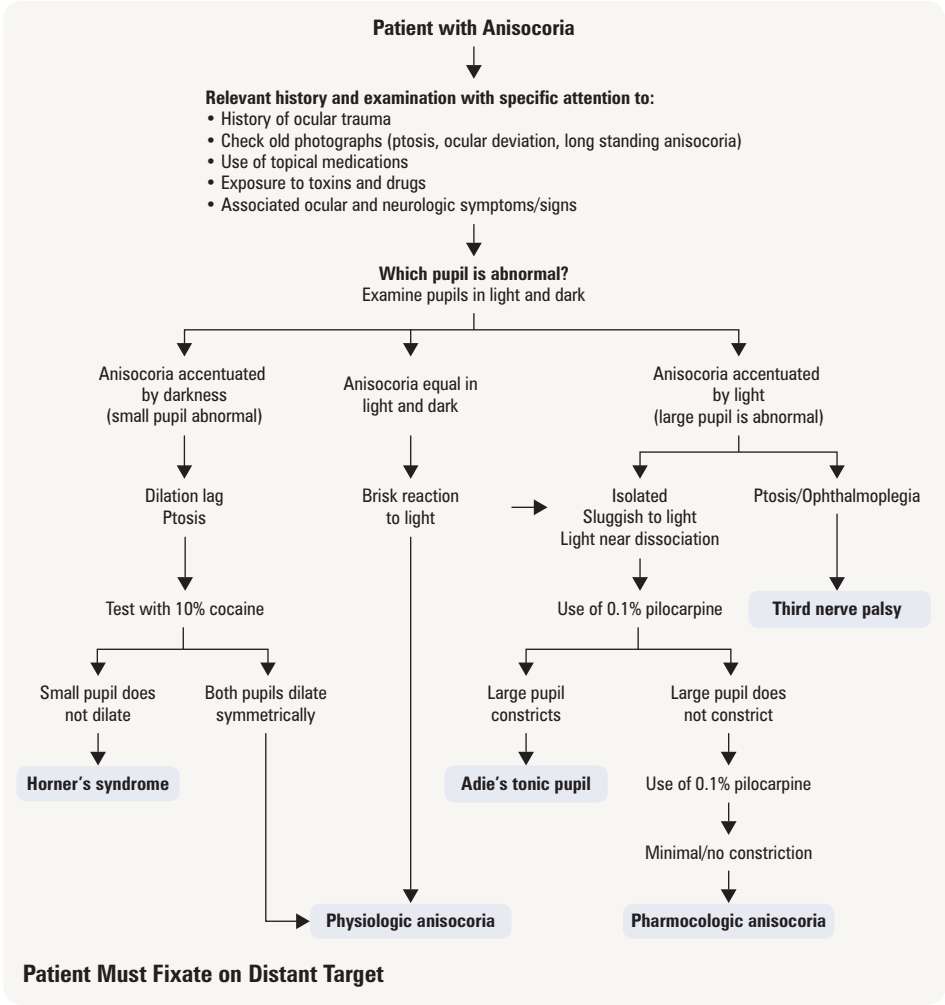
### Local Disorders of Iris

- posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
- ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o'clock positions resulting in a vertically oval pupil that reacts poorly to light
- trauma (e.g. post-intraocular surgery)

### Anisocoria

- unequal pupil size
- idiopathic/physiologic anisocoria
  - 20% of population
  - round, regular, <1 mm difference
  - pupils reactive to light and accommodation
  - responds normally to mydriatics/miotics
- post eye surgery
- see Table 7 for other causes of anisocoria





**Figure 22. Approach to anisocoria**  
Reproduced with permission from: Kedar S, Biousse V, Newman NJ. *Approach to the patient with anisocoria*. In: UpToDate, Rose, BD (ed), UpToDate, Waltham, MA, 2011. Copyright 2011 UpToDate, Inc. For more information visit [www.uptodate.com](http://www.uptodate.com).

**Table 7. Summary of Conditions Causing Anisocoria**

Features	Site of Lesion	Light and Accommodation	Anisocoria	Mydriatics/Miotics	Effect of Pilocarpine
<b>ABNORMAL MIOTIC PUPIL (impaired pupillary dilation)</b>					
<b>Argyll-Robertson Pupil</b>	Irregular, usually bilateral	Midbrain	Poor in light; better to accommodation		Dilates/Constricts
<b>Horner's Syndrome</b>	Round, unilateral, ptosis, anhydrosis, pseudoenophthalmos	Sympathetic system	Both brisk	Greater in dark	Dilates/Constricts
<b>ABNORMAL MYDRIATIC PUPIL (impaired pupillary constriction)</b>					
<b>Adie's Tonic Pupil</b>	Irregular, larger in bright light	Ciliary ganglion	Poor in light, better to accommodation	Greater in light	Dilates/Constricts Constricts (hypersensitivity to dilute pilocarpine)
<b>CN III Palsy</b>	Round	Superficial CN III	± fixed (acutely) at 7-9 mm	Greater in light	Dilates/Constricts Constricts
<b>Mydriatic Pupil</b>	Round, uni- or bilateral	Iris sphincter	Fixed at 7-8 mm	Greater in light	No effect Will not constrict

## Dilated Pupil (Mydriasis)

### Sympathetic Stimulation

- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

### Parasympathetic Understimulation

- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, diabetes mellitus (may spare pupil), trauma
  - CN III palsy will respond to drugs (e.g. pilocarpine), unlike a pupil dilated from medication (mydriatics)

### Acute Angle-Closure Glaucoma

- fixed, mid-dilated pupil

### Adie's Tonic Pupil

- 80% unilateral, females > males
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- if decreased deep tendon reflexes may be Adie's syndrome
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
  - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- long-standing Adie's pupils are smaller than unaffected eye

### Trauma

- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

## Constricted Pupil (Miosis)

### Senile Miosis

- decreased sympathetic stimulation with age

### Parasympathetic Stimulation

- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - cholinesterase inhibitor: phospholine iodide
  - opiates, barbiturates

### Horner's Syndrome

- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis, anhidrosis of ipsilateral face/neck
- application of cocaine 4-10% (blocks reuptake of noradrenaline) to eye does not result in pupil dilation (vs. physiologic anisocoria), therefore confirms diagnosis
- hydroxyamphetamine 1% (stimulates noradrenaline release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- postganglionic lesions result in denervation hypersensitivity, which will cause pupil to dilate with 0.125% adrenaline, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumour, Pancoast tumour, goiter, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabes dorsalis, cervical vertebral fractures

### Iritis

- miotic pupil initially
- later, may be irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light



CN III palsy with pupillary involvement may be associated with a posterior communicating artery aneurysm.

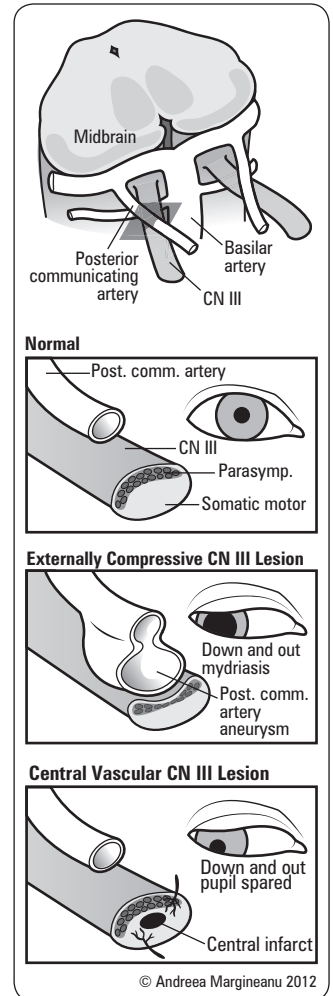


Figure 23. CNIII lesions with and without mydriasis



### Horner's MAP

Miosis  
Anhidrosis  
Ptosis

**Argyll-Robertson Pupil**

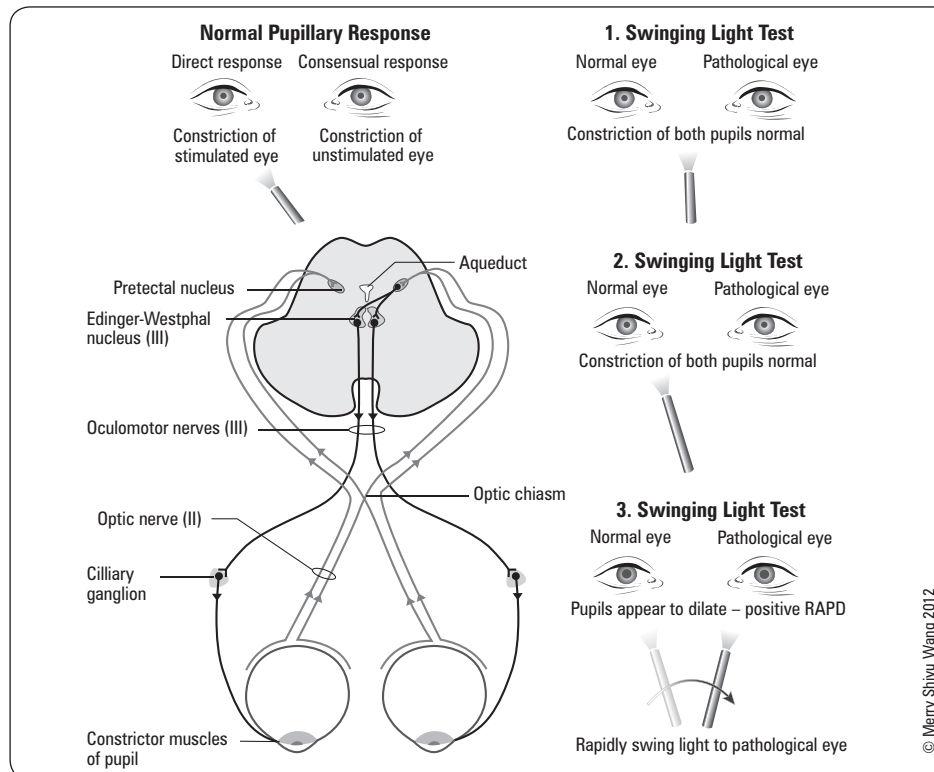
- both pupils irregular and <3 mm in diameter,  $\pm$  ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of neurosyphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)

**Other Causes**

- optic neuritis, retinal lesions

**Argyll-Robertson Pupil****ARP-PRA**

Accommodation Reflex Present  
Pupillary Reflex Absent

**Relative Afferent Pupillary Defect (RAPD)**

Cataracts never produce an RAPD.



It is possible to have RAPD and normal vision at the same time, e.g. in damaged superior colliculus caused by thalamic hemorrhage.



Differentiate RAPD from physiologic pupillary athetosis ("hippus"), which is rapid, rhythmic fluctuations of the pupil, with equal amplitude in both eyes.

**Figure 24. Relative afferent pupillary defect**

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light, caused by a lesion in visual afferent (sensory) pathway anterior to optic chiasm
- DDx: large retinal detachment, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, optic neuritis (most common)
- does not occur with media opacity (e.g. corneal edema, cataracts)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffected eye to the affected eye, "paradoxical" dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides
- if the defect is bilateral there is no RAPD, as dilation is measured relative to the other eye

## Malignancies

- uncommon site for 1° malignancies
- eye usually affected secondarily by cancer or cancer treatments
- see *Retinoblastoma*, OP41

### Lid Carcinoma



#### Etiology

- basal cell carcinoma (rodent ulcer) (90%)
  - spread via local invasion, rarely metastasizes
  - ulcerated centre, indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
  - spread via local invasion, may also spread to nodes and metastasize
  - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
  - often masquerades as chronic blepharitis or recurrent chalazion
  - highly invasive, metastasize
- Kaposi's sarcoma, malignant melanoma, Merkel cell tumour, metastatic tumour

#### Treatment

- incisional or excisional biopsies
- may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
- surgical reconstruction

### Malignant Melanoma

- most common 1° intraocular malignancy in adults
- more prevalent in Caucasians
- arise from uveal tract, 90% choroidal melanoma
- hepatic metastases predominate

#### Treatment

- imaging to investigate spread
- depending on the size of the tumour, either radiotherapy, enucleation, limited surgery

### Metastases

- most common intraocular malignancy in adults
- most commonly from breast and lung in adults, neuroblastoma in children
- usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
- may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

#### Treatment

- local radiation, chemotherapy
- enucleation if blind, painful eye

## Ocular Manifestations of Systemic Disease

### HIV/AIDS

- up to 75% of patients with AIDS have ocular manifestations

#### External Ocular Signs

- Kaposi's sarcoma
  - 2° to human herpes virus 8 (HHV-8), affects conjunctiva of lid or globe
  - numerous vascular skin malignancies
  - DDx: subconjunctival hemorrhage (non-clearing), hemangioma
- multiple molluscum contagiosum
- herpes simplex keratitis
- herpes zoster keratitis

## Retina

- HIV retinopathy (most common)
  - cotton wool spots in >50% of HIV patients
  - intraretinal hemorrhage
- CMV retinitis
  - ocular opportunistic infection that develops in late stages of HIV when severely immunocompromised (CD4 count  $\leq 50$ )
  - a necrotizing retinitis, with retinal hemorrhage and vasculitis, “brushfire” or “pizza pie” appearance
  - presents with scotomas (macular involvement and retinal detachment), blurred vision, and floaters
  - untreated infection will progress to other eye in 4-6 wk
  - treatment: virostatic agents (e.g. gancyclovir or foscarnet) via IV or intravitreal injection
- necrotizing retinitis
  - from herpes simplex virus, herpes zoster, toxoplasmosis
- disseminated choroiditis
  - *Pneumocystis carinii*, *Mycobacterium avium intracellulare*, *Candida*



## Other Systemic Infections

- herpes zoster
  - see *Herpes Zoster*, OP19
- candidal endophthalmitis
  - fluffy, white-yellow, superficial retinal infiltrate that may eventually result in vitritis
  - may present with inflammation of the anterior chamber
  - treatment: systemic amphotericin B, oral fluconazole
- toxoplasmosis
  - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous infiltration (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by *Toxoplasma gondii* protozoa transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folinic acid, or clindamycin. Consider adding steroids if severe inflammation (vitritis, macular or optic nerve involvement)

## Diabetes Mellitus (DM)

- see *Endocrinology*, E6
- most common cause of blindness in young people in North America
- consider DM if unexplained retinopathy, cataract, extraocular muscle palsy, optic neuropathy, sudden change in refractive error
- loss of vision due to:
  - progressive microangiopathy leading to macular edema
  - progressive diabetic retinopathy  $\rightarrow$  neovascularization  $\rightarrow$  traction  $\rightarrow$  retinal detachment and vitreous hemorrhage
  - rubeosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia



Macular edema is the most common cause of visual loss in patients with background DR.

## DIABETIC RETINOPATHY (DR)

### Background

- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening of basement membrane)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

### Classification

- **non-proliferative:** increased vascular permeability and retinal ischemia
  - microaneurysms
  - dot and blot hemorrhages
  - hard exudates (lipid deposits), non-specific for DR
  - macular edema
- **advanced non-proliferative (or pre-proliferative):**
  - non-proliferative findings plus:
    - ♦ venous beading (in  $\geq 2$  of 4 retinal quadrants)
    - ♦ intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
      - IRMA: dilated, leaky vessels within the retina
    - ♦ cotton wool spots (nerve fibre layer infarcts)



### Presence of DR in:

#### Type 1 DM

- 25% after 5 yr
- 60% after 10 yr
- >80% after 15 yr

#### Type 2 DM

- 20% at time of diagnosis
- 60% after 20 yr

- **proliferative:**

- 5% of patients with diabetes will reach this stage
- neovascularization of iris, disc, retina to vitreous
  - ♦ neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
  - ♦ vitreous hemorrhage from bleeding, fragile new vessels, fibrous tissue can contract causing tractional retinal detachment
- high risk of severe visual loss 2° to vitreous hemorrhage, retinal detachment

### Screening Guidelines for Diabetic Retinopathy

- type 1 DM
  - screen for retinopathy beginning annually 5 yr after disease onset
  - annual screening indicated for all patients over 12 yr and/or entering puberty
- type 2 DM
  - initial examination at time of diagnosis, then annually
- pregnancy
  - ocular exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
  - gestational diabetics are not at risk for diabetic retinopathy

### Treatment

- Diabetic Control and Complications Trial (DCCT)
  - tight control of blood sugar decreases frequency and severity of microvascular complications
- blood pressure control
- focal laser for clinically significant macular edema, intravitreal injection of corticosteroid or anti-VEGF for foveal involved diabetic macular edema
- panretinal laser photocoagulation for proliferative diabetic retinopathy: reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
- vitrectomy for non-clearing vitreous hemorrhage and retinal detachment in proliferative diabetic retinopathy
- vitrectomy before vitreous hemorrhage does not improve the visual prognosis

### Lens Changes

- earlier onset of senile nuclear sclerosis and cortical cataract
- may get hyperglycemic cataract, due to sorbitol accumulation (rare)
- changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3-4 diopters

### Extraocular Muscle Palsy

- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- may involve CN IV and VI
- usually recover within few months

### Optic Neuropathy

- visual acuity loss due to infarction of optic disc/nerve



Clinically significant macular edema is defined as thickening of the retina at or within 500  $\mu\text{m}$  of the centre of the macula.



**The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-term Complications of Insulin-dependent Diabetes Mellitus**  
*NEJM* 1993;329:977-986

DCCT trial shows intensive glycemic control will reduce the risk of diabetic retinopathy by 76%, and reduce the risk of worsening diabetic retinopathy by 54%.



**Early Treatment Diabetic Retinopathy Study Aspirin® Effects on Mortality and Morbidity in Patients with Diabetes Mellitus**  
*ETDRS Report 14. JAMA* 1992;268:1292-1300

#### ETDRS Demonstrates

- No benefit of Aspirin® in reduction in risk of progression of diabetic retinopathy, no increased risk of hemorrhage either
- Early treatment using panretinal photocoagulation reduces the risk of visual loss
- Clinically significant macula edema should be treated by focal laser



**Expanded 2-year Follow-up of Ranibizumab plus Prompt or Deferred Laser or triamcinolone plus Prompt Laser for Diabetic Macular Edema**  
*Ophthalmology* 2011;118:609-614

Ranibizumab (Lucentis®) with prompt or deferred laser is more effective than intravitreal corticosteroid injections + laser or laser alone with sustained efficacy up to 24 mo.

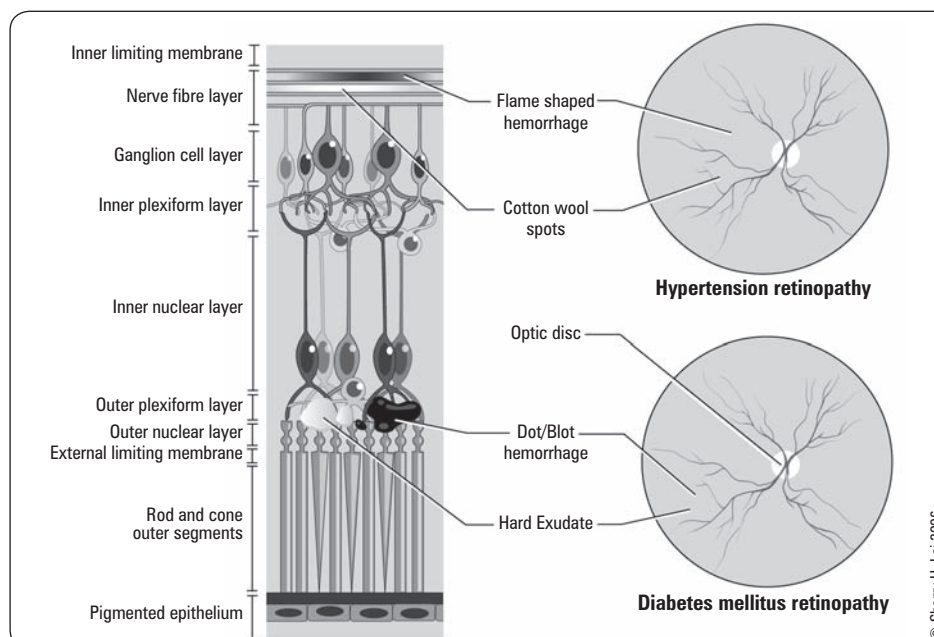


Figure 25. DM vs. HTN retinopathy



## Hypertension

- retinopathy is the most common ocular manifestation
- chronic HTN retinopathy: arteriovenous (AV) nicking, blot retinal hemorrhages, microaneurysms, cotton wool spots
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema

**Table 8. Keith-Wagener-Barker Classification**

<b>Group 1</b>	Mild arterial narrowing
<b>Group 2</b>	Obvious arterial narrowing with focal irregularities
<b>Group 3</b>	Group 2 characteristics plus: Cotton-wool spots Hemorrhage and/or exudate
<b>Group 4</b>	Group 3 plus papilledema



## Multiple Sclerosis (MS)

- see [Neurology](#), N46

### Clinical Features

- blurred vision and decreased colour vision: 2° to optic neuritis
- central scotoma: due to damage to papillomacular bundle of retinal nerve fibres
- diplopia: 2° to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

### Treatment

- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation as this increases likelihood of eventual development of MS



#### Optic Neuritis Treatment Trial (ONTT)

**Optic Neuritis Study Group: The Optic Neuritis Treatment Trial. Three-year follow-up Results**  
*Arch Ophthalmol* 1995;113:136-137

ONTT recruited patients with acute new onset optic neuritis and studied outcome of three treatment regimes: oral steroid x 14 d, IV steroid x 3 d + oral steroid x 11 d, and placebo x 14 d. They found that oral steroid increases risk of recurrence, IV + oral steroid expedites recovery, and "no treatment" was a viable therapeutic option. Furthermore, brain MRI is most valuable in prediction of onset of MS.

## TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

## Graves' Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur 2° to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

### Clinical

- initial inflammatory phase is followed by a quiescent cicatricial phase

### Treatment

- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, proptosis and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides



The most common cause of unilateral or bilateral proptosis in adults is Graves' disease.



#### Progression of Signs and Symptoms of Graves' Ophthalmopathy

##### NO SPECS

No signs/symptoms  
Only signs (lid retraction, lid lag)  
Soft tissue swelling (periocular edema)  
Proptosis (exophthalmos)  
Extraocular muscle weakness (causing diplopia)  
Corneal exposure  
Sight loss

## Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjogren's syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)

## Giant Cell Arteritis (GCA)/Temporal Arteritis

- see [Rheumatology](#), RH20

### Clinical

- more common in women >60 yr
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and past medical history of polymyalgia rheumatica
- ischemic optic atrophy
  - 50% lose vision in other eye if untreated

### Diagnosis

- temporal artery biopsy + increased ESR (ESR can be normal, but likely 80-100 in first hour), CRP
- if biopsy of one side is negative, biopsy the other side

### Treatment

- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation (**DO NOT WAIT TO TREAT**)



#### ESR in Temporal Arteritis

Males > age/2

Females > (age + 10) / 2



#### Does this Patient have Temporal Arteritis?

JAMA 2002;287:92-101

**Rule in:** jaw claudication and diplopia on history, temporal artery beading, prominence of the artery and tenderness over the artery on exam.

**Rule out:** no temporal artery abnormalities on exam, normal ESR.

## Sarcoidosis

- granulomatous uveitis with large “mutton fat” keratic precipitates and posterior synechiae
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

### Treatment

- steroids and mydriatics

## Pediatric Ophthalmology

### Strabismus

- ocular misalignment in one or both eyes, found in 3% of children
- object not visualized simultaneously by fovea of each eye
- terms used to describe strabismus depend upon:
  - direction of deviation relative to the fixating eye
  - conditions under which it presents: ‘latent’, ‘manifest’ misalignment
  - change with the position of gaze: ‘comitant’ (usually nonparalytic), ‘incomitant’ (usually occurs with paralytic or restrictive strabismus)
- often presents with parental concern about a wandering eye, crossing eye, or poor vision
- elicit a detailed family history of strabismus, amblyopia, type of eyeglasses and history of wear, extraocular muscle surgery or other eye surgery, and genetic diseases to identify children at higher risk
- distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism, markedly positive or negative angle  $\kappa$ )
- complications: amblyopia, cosmesis

### HETEROTROPIA

- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

### Types

- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = “crossed-eyes”; exotropia = “wall-eyed”

### Differentiate from Pseudostrabismus

- prominent epicanthal folds: give appearance of esotropia but Hirschberg test is normal, more common in Asians
- markedly elevated angle  $\kappa$  (the angle formed by the pupillary axis and the visual axis at the centre of the pupil)
  - caused by the failure of optical axis of the eye and the visual axis to coincide
  - a small positive (up to 5°) angle  $\kappa$  is physiologic
  - a large positive angle  $\kappa$  (nasally deviated fovea) simulates eso-appearance
  - a large negative angle  $\kappa$  (temporally deviated fovea) gives an exo-appearance



Strabismus in children under 4 mo of age sometimes resolves, particularly if the deviation is intermittent, variable or measures less than 40 prism diopters

### Tests

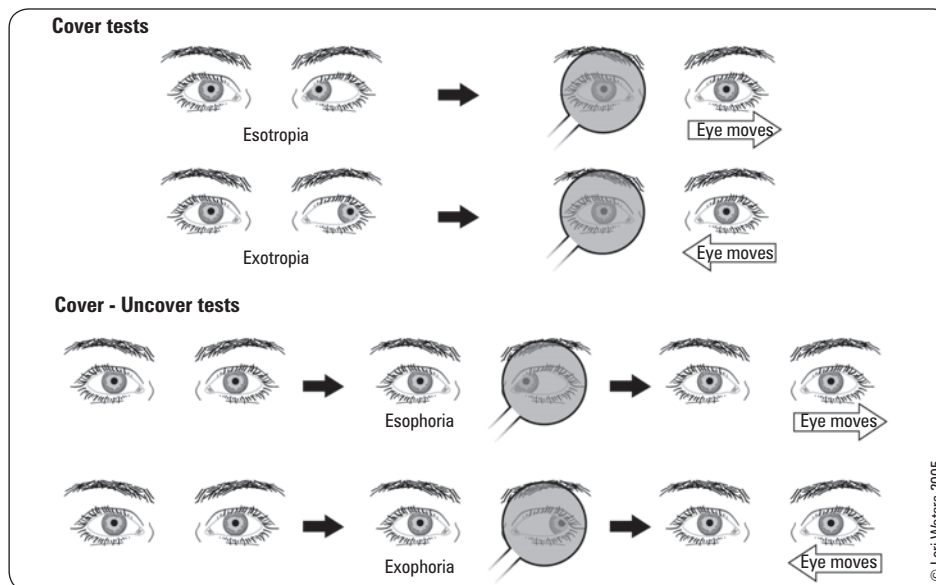
- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - light reflex lateral to central cornea indicates esodeviation; light reflex medial to central cornea indicates exodeviation
  - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle  $\kappa$ )
- cover test (Figure 26)
- the deviation can be quantified using prisms

### HETEROPHORIA

- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- Hirschberg test will be normal (light reflexes symmetrical)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue)

### Tests

- cover-uncover test
- alternate cover test
  - alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - maintain cover over one eye for 2-3 s before rapidly shifting to other eye



All children with strabismus and/or possible reduced vision require prompt referral to an ophthalmologist.

Figure 26. Cover and cover-uncover tests for detection of tropias and phorias

Table 9. Paralytic vs. Non-Paralytic Strabismus

Clinical Characteristics	Paralytic Strabismus	Nonparalytic Strabismus
<b>Definition</b>	Incomitant strabismus	Concomitant strabismus
<b>Onset</b>	Often sudden but may be gradual or congenital	Usually gradual or shortly after birth; rarely sudden
<b>Age of onset</b>	Any age; most often acquired	Usually during infancy
<b>Etiology</b>	Reduction or restriction in range of eye movements due to: <ul style="list-style-type: none"> <li>• Neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumour, trauma</li> <li>• Muscular: myasthenia gravis (neuromuscular junction pathology), Graves' disease</li> <li>• Structural: restriction or entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall</li> </ul>	Develops early in childhood No restriction in range of eye movements Monocular, alternating, or intermittent
<b>Diplopia</b>	Common	Uncommon; image from the misaligned eye is suppressed (see <i>Amblyopia</i> , OP40)
<b>Visual acuity in other eye</b>	Usually unaffected in the other eye, unless CN II is involved	Deviated eye may become amblyopic if not treated when the child is young Amblyopia treatment rarely successful after age 8-10 yr Amblyopia usually does not develop if child has alternating strabismus or intermittency, which allows neural pathways for both eyes to develop
<b>Possibility of amblyopia</b>	Uncommon	Common
<b>Neurologic findings or systemic disease</b>	May be present	Usually absent

**Accommodative Esotropia**

- normal response to approaching object is the triad of the near reflex: convergence, accommodation and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 yr
- usually reversible with correction of refractive error

**Non-accommodative Esotropia**

- accounts for 50% of childhood strabismus
- most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

## Amblyopia

**Definition**

- a neurodevelopmental visual disorder with unilateral (or less commonly, bilateral) reduction of best corrected visual acuity that cannot be attributed only and directly to the effect of a structural abnormality of the eye. It is caused by abnormal visual experience early in life and cannot be remedied immediately by spectacle glasses alone
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia). Other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors), and concomitant structural ocular problems

**Detection**

- “Holler Test”: young child upset if good eye is covered
- quantitative visual acuity by age 3-4 yr using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
- prognosis: 90% will have good vision restored and maintained if treated <4 yr old

**Etiology and Management**

- strabismus
  - correct with glasses for accommodative esotropia (50% of children experience relief of their esotropia with glasses and will not require surgery)
  - occlusion of unaffected eye forces brain to use previously strabismic eye; aims to bring vision in previously suppressed eye to normal before surgery
  - surgery: recession (weakening) – moving muscle insertion further back on the globe; or resection (strengthening) – shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until approximately age 8 yr
- anisometropia
  - amblyopia usually in the more hyperopic eye
  - the more emmetropic (normal refraction) eye receives a clear image while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if visual acuity difference persists after 4-8 wk of using glasses
- deprivation amblyopia
  - occlusion due to ptosis, cataract, retinoblastoma, corneal opacity
  - occlusion amblyopia: prolonged patching of good eye may cause it to become amblyopic

**Occlusion Therapy**

- patching the good eye to force the brain to use the non-dominant eye and redevelop its vision
- atropine cycloplegic drops to impair accommodation and blur vision of the better seeing eye

**Risks**

- permanent loss of vision in the affected eye
- possibility of injury to ‘remaining’ good eye
  - safety glasses or polycarbonate lenses recommended if visual acuity in worse eye is less than 20/50
- loss of stereopsis

## Leukocoria

- white reflex (red reflex is absent)

### Differential Diagnosis

- cataract
- retinoblastoma
- retinal coloboma
- ROP
- persistent hyperplastic primary vitreous
- Coat's disease (exudative retinal telangiectasis)
- toxocariasis
- retinal detachment



## Retinoblastoma

- most common primary intraocular malignancy in children
- incidence: 1/15 000; sporadic or genetic transmission; screening of siblings/offspring essential
- unilateral or bilateral (in 1/3 of cases)
- malignant – direct or hematogenous spread
- diagnosis
  - often presents with leukocoria or strabismus
  - U/S or CT scan may demonstrate calcified mass (present in most cases)

### Treatment

- radiotherapy, chemotherapy combined with laser, cryopexy, and/or enucleation



## Retinopathy of Prematurity (ROP)

- vasoproliferative retinopathy that is a major cause of blindness in the developed world

### Risk Factors

- non-black race (black infants have lower risk of developing ROP)
- low gestational age, birth weight <1500 g
- high oxygen exposure after birth

### Classification (ROP Staging)

- stage 1: faint demarcation line at the junction between the vascularized and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial retinal detachment (4A: macula “on”; 4B: macula “off”)
- stage 5: total retinal detachment
- plus (+) disease: dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with 5 continuous or 8 cumulative clock hours of ROP involvement

### Treatment

- threshold disease is treated with cryotherapy or laser (laser is now the standard treatment, with better refractive outcome), off label anti-VEGF intravitreal injections (see sidebar)
- ROP beyond threshold level is either watched carefully (usually stage 4A) or treated with vitrectomy/scleral buckle

### Prognosis

- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

## Nasolacrimal System Defects

- congenital obstruction of the nasolacrimal duct (failure of canalization), usually occurs at 1-2 mo of age
- epiphora, crusting, discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac
- treatment: massage over lacrimal sac at medial corner of eyelid
- vast majority spontaneously resolve in 9-12 mo, otherwise consider referral for duct probing



### Retinal Zones (Figure 27)

- Zone I: circle with radius twice the distance from the disc to the macula (most difficult to treat)
- Zone II: annulus from zone I to nasal extent of retina (nasal ora serrata)
- Zone III: remaining retina

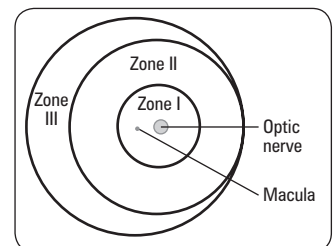


Figure 27. Zones of the retina in ROP



### Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity (ROP)

NEJM 2011;364:603-615

**Study:** Randomized controlled clinical trial.

**Patients:** 150 infants born at gestational age ≤30 wk and birth weight ≤1500 g.

**Intervention:** Randomized to conventional laser therapy or intravitreal bevacizumab monotherapy.

**Main Outcome:** Recurrence of ROP in one or both eyes requiring retreatment before 54 wk postmenstrual age.

**Results:** ROP recurrence was lower in the bevacizumab group [6 of 140 eyes (4%)] versus the laser-therapy group [32 of 146 eyes (22%)] ( $p = 0.002$ ). A significant treatment effect was found for zone I retinopathy of prematurity ( $p = 0.003$ ).

**Conclusions:** Intravitreal bevacizumab monotherapy is beneficial for infants with zone I state 3+ ROP and allows continued development of peripheral retinal vessels following treatment.

## Ophthalmia Neonatorum

- newborn conjunctivitis in first month of life
- causes:
  - toxic: silver nitrate, erythromycin
  - infectious: bacterial (e.g. *Neisseria gonorrhoeae* – most common, *Chlamydia trachomatis*), herpes simplex virus
- diagnose using stains and cultures
- treatment: systemic antibiotics with possible hospitalization if infectious etiology
- topical prophylaxis, most commonly with erythromycin (or silver nitrate), is required by law at birth



Gonococcal infection is the most serious threat to sight as it can rapidly penetrate corneal epithelium, causing corneal ulceration.

## Congenital Glaucoma

- due to inadequate development of the filtering mechanism of the anterior chamber angle

### Clinical Features

- cloudy cornea, increased IOP
- photophobia, epiphora
- buphthalmos (large cornea, “ox eye”, 2° to increased IOP), blepharospasm

### Treatment

- filtration surgery is required soon after birth to prevent blindness



Epiphora in children – r/o congenital glaucoma!

## Ocular Trauma

### Blunt Trauma

- caused by blunt object such as fist, squash ball
- history: injury, ocular history, drug allergy, tetanus status
- exam: VA first, pupil size and reaction, EOM (diplopia), external and slit lamp exam, ophthalmoscopy
- if VA normal or slightly reduced, globe less likely to be perforated
- if VA reduced may be perforated globe, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion – detect with fluorescein staining and cobalt blue filter using slit lamp or ophthalmoscope
- anterior chamber: assess depth, hyphema, hypopyon
- iris: prolapse, iritis
- lens: cataract, dislocation
- retinal tear/detachment



Always test VA first – medicolegal protection.



### Refer if you observe any of these signs

- Decreased VA
- Shallow anterior chamber
- Hyphema
- Abnormal pupil
- Ocular misalignment
- Retinal damage



### Management of Suspected Globe Rupture

**CAN'T** forget  
CT orbits  
Ancef (cefazolin) ± Aminoglycoside IV  
NPO  
Tetanus status



### Post-traumatic Infectious Endophthalmitis

*Surv Ophthalmol* 2011;56:214-251  
Delayed primary repair (>24 h after open globe injury) increases risk for post-traumatic endophthalmitis in the absence of an intraocular foreign body (IOFB).  
If IOFB present, early vitrectomy and IOFB removal must be performed within 24 h of injury.  
Extreme pain with hypopyon and vitritis indicate endophthalmitis until proven otherwise, and samples must be obtained.  
Treat with empirical intravitreal and intravenous antibiotic guided by nature of trauma, and adjust based on culture.

### Penetrating Trauma

- include ruptured globe ± prolapsed iris, intraocular foreign body
- rule out intraocular foreign body, especially if history of “metal striking metal”, orbit CT
- initial management: REFER IMMEDIATELY
  - ABCs
  - don't press on eye globe!
  - don't check IOP if possibility of globe rupture
  - check vision, diplopia
  - apply rigid eye shield to minimize further trauma
  - keep head elevated 30-45° to keep IOP down
  - keep NPO
  - tetanus status
  - give IV antibiotics
    - ♦ selecting appropriate agents depends on the mechanism of injury. Gram positive bacteria are more commonly involved than gram negatives. Retained intraocular foreign objects increase the risk of infections with *Bacillus* species, whereas exposure to vegetable matter increased the risk of a fungal etiology



## Hyphema

- blood in anterior chamber often due to damage to root of the iris
- may occur with blunt trauma

### Treatment

- refer to ophthalmology
  - shield and bedrest x 5 d or as determined by ophthalmologist
  - sleep with head upright
- may need surgical drainage if hyphema persists or if re-bleed

### Complications

- risk of re-bleed highest on days 2-5, resulting in 2° glaucoma, corneal staining, and iris necrosis
- never prescribe Aspirin®, as it increases the risk of a re-bleed



#### Shaken Baby Syndrome

Syndrome of findings characterized by absence of external signs of abuse with respiratory arrest, seizures, or coma. Ocular exam findings are important diagnostically for Shaken Baby Syndrome. These findings include extensive retinal and vitreous hemorrhages that occur during the shaking process and are extremely rare in accidental trauma. A detailed fundoscopic exam or an ophthalmology referral should be conducted for all infants in whom abuse is suspected.

## Blow-Out Fracture

- see [Plastic Surgery](#), PL31
- blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
- orbital rim remains intact
- inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
- infraorbital nerve courses along the floor of the orbit and may be damaged

### Clinical Features

- pain and nausea at time of injury
- diplopia, restriction of EOM
- infraorbital and upper lip paresthesia (CN V2)
- enophthalmos (sunken eye), periorbital ecchymoses

### Investigations

- plain films: Waters' view and lateral
- CT: anteroposterior and coronal view of orbits

### Treatment

- refrain from coughing, blowing nose
- systemic antibiotics may be indicated
- surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
- may delay surgery if the diplopia improves



#### Classic Signs of Blow-Out

- Enophthalmos
- Decreased upgaze (IR trapped)
- Cheek anesthetized (infraorbital nerve trapped)

## Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks (thus, very guarded prognosis)

### Treatment

- immediately irrigate at site of accident with water or buffered solution
  - IV drip for at least 20-30 min with eyelids retracted in emergency department
  - swab upper and lower fornices to remove possible particulate matter
- do not attempt to neutralize because the heat produced by the reaction will damage the cornea
- cycloplegic drops to decrease iris spasm (pain) and prevent 2° glaucoma (due to posterior synechiae formation)
- topical antibiotics and patching
- topical steroids (by ophthalmologist) to decrease inflammation, use for less than 2 wk (in the case of a persistent epithelial defect)



Fluorescein lights up alkali so you can detect it and assess whether it has been removed.

## Surgical Ophthalmology

- **dacryocystorhinostomy (DCR)**: excision of bone covering the nasolacrimal sac to restore tear drainage
- **LASIK (laser-assisted in-situ keratomileusis)**: a microkeratome is used to create a corneal flap followed by laser remodeling of the stroma to correct refractive error
- **trabeculectomy**: creation of a new outflow tract from anterior chamber to under conjunctiva; fibrosis prevented with mitomycin C or 5-FU injection during surgery
- **phacoemulsification (cataract extraction)**: the use of ultrasonic waves to break up and aspirate a cataract followed by replacement with an artificial lens implant
- **vitrectomy**: the use of small trochars to enter the posterior segment and remove vitreous; commonly used to treat vitreous hemorrhage and retinal detachment
- **pneumatic retinopexy**: intraocular injection of air or an expandable gas in order to tamponade a retinal break for repair of retinal detachment
- **scleral buckle**: a band is secured on the outside of the globe that indents the eye wall, thereby relieving vitreous traction on the retina around any tears/holes and allowing the tears/holes to remain sealed

## Ocular Drug Toxicity

**Table 10. Drugs with Ocular Toxicity**

Amiodarone	Corneal microdeposits and superficial keratopathy (vortex keratopathy) Rare: ischemic optic neuropathy
Atropine, benzotropine	Pupillary dilation (risk of angle closure glaucoma)
Bisphosphonates (Fosamax®, Actonel®)	Inflammatory eye disease (iritis, scleritis, episcleritis)
Chloroquine, hydroxychloroquine	Bull's eye maculopathy Vortex keratopathy
Chlorpromazine	Anterior subcapsular cataract
Contraceptive pills	Decreased tolerance to contact lenses Migraine Optic neuritis Central vein occlusion
Digitalis	Yellow vision Blurred vision
Ethambutol	Optic neuropathy
Haloperidol (Haldol®)	Oculogyric crises Blurred vision
Indomethacin	Superficial keratopathy
Interferon	Retinal hemorrhages and cotton wool spots
Isoniazid	Optic neuropathy
Nalidixic acid	Papilledema
Steroids	Posterior subcapsular cataracts Glaucoma Papilledema (systemic steroids) Increased severity of HSV infections (geographic ulcers) Predisposition to fungal infections
Sulphonamides, NSAIDs	Stevens-Johnson syndrome
Tamsulosin (Flomax®)	Intraoperative Floppy Iris Syndrome, which can complicate cataract surgery
Tetracycline	Papilledema (associated with pseudotumour cerebri)
Thioridazine	Pigmentary degeneration of retina
Vigabatrin	Retinal deposition with macular sparing, peripheral visual field loss
Vitamin A intoxication	Papilledema
Vitamin D intoxication	Band keratopathy

## Common Medications

### TOPICAL OCULAR DIAGNOSTIC DRUGS

#### Fluorescein Dye

- water soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope or slit lamp)
- absorbed in areas of epithelial loss (ulcer or abrasion)
- also stains mucus and contact lenses

#### Rose Bengal Stain

- stains devitalized epithelial cells and mucus

### Anesthetics

- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore **NEVER** prescribe

### Mydriatics

- dilate pupils
- two classes
  - cholinergic blocking (e.g. tropicamide – Mydracyl®)
    - ♦ dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    - ♦ indications: refraction, ophthalmoscopy, therapy for iritis
  - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    - ♦ stimulate pupillary dilator muscles, no effect on accommodation
    - ♦ usually used with tropicamide for additive effects
    - ♦ side effects: hypertension, tachycardia, arrhythmias

**Table 11. Mydriatic Cycloplegic Drugs and Duration of Action**

Drugs	Duration of Action
Tropicamide (Mydracyl®) 0.5%, 1%	4-5 h
Cyclopentolate HCl 0.5%, 1%	3-6 h
Homatropine HBr 1%, 2%	3-7 d
Atropine sulfate 0.5%, 1%	1-2 wk
Scopolamine HBr 0.25%, 5%	1-2 wk

## GLAUCOMA MEDICATIONS

**Table 12. Glaucoma Medications**

Drug Category	Dose	Effect	Comment/Side Effects
<b>α-Agonist</b> <b>Non-selective</b> <ul style="list-style-type: none"> <li>• epinephrine HCl 1% (Epifrin®)</li> <li>• dipivalyl epinephrine 0.1% (Propine®)</li> </ul> <b>α<sub>2</sub>-selective</b> <ul style="list-style-type: none"> <li>• brimonidine 0.2% (Alphagan®)</li> <li>• apraclonidine 0.5% (Lopidine®)</li> </ul>	1 gtt OS/OD bid/tid	1. Non-selective: ↓ aqueous production + ↑ TM outflow 2. Selective: ↓ aqueous production + ↑ uveoscleral outflow	1. Non-selective: mydriasis, macular edema, tachycardia 2. Selective: contact allergy, hypotension in children
<b>β-Blocker</b> <b>Non-selective</b> <ul style="list-style-type: none"> <li>• timolol (Timoptic®)</li> <li>• levobunolol (Betagan®)</li> </ul> <b>β<sub>1</sub>-selective</b> <ul style="list-style-type: none"> <li>• betaxolol (Betoptic®)</li> </ul>	1 gtt OS/OD qd/bid	↓ aqueous production	<b>Bronchospasm (caution in asthma/COPD)</b> ↑ CHF Bradycardia Hypotension Depression Heart block Impotence
<b>Carbonic Anhydrase Inhibitor</b> <ul style="list-style-type: none"> <li>• dorzolamide (Trusopt®)</li> <li>• brinzolamide (Azopt®)</li> <li>• oral: acetazolamide (Diamox®)</li> </ul>	1 gtt OS/OD tid Diamox®: 500 mg PO bid	↓ aqueous production	<b>Must ask about sulfa allergy</b> Generally local side effects with topical preparations Oral: diuresis, fatigue, paresthesias, GI upset, etc.
<b>Parasympathomimetic</b> (cholinergic stimulating) <ul style="list-style-type: none"> <li>• pilocarpine (Pilopine®)</li> <li>• carbachol (Isopto Carbachol®)</li> </ul>	1-2 gtt OS/OD tid/qid	↑ TM outflow	Miosis ↓ night vision ↑ GI motility Brow ache Headache ↓ heart rate
<b>Prostaglandin Analogues</b> <ul style="list-style-type: none"> <li>• latanoprost (Xalatan®)</li> <li>• travaprost (Travatan®)</li> <li>• bimatoprost (Lumigan®)</li> </ul>	1 gtt OS/OD qhs	↑ uveoscleral outflow (uveoscleral responsible for 20% of drainage)	Iris colour change Periorbital skin pigmentation Lash growth Conjunctival hyperemia

Cosopt® = timolol + dorzolamide; Xalatan® = timolol + latanoprost; Combigan® = timolol + brimonidine; DuoTrav® = timolol + travaprost; gtt = drop, gttS = drops

## WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

### Vascular Endothelial Growth Factors (VEGF) Inhibitors

- block vascular endothelial growth factor which prevents ocular angiogenesis and further development of choroidal neovascularization
- administered via intravitreal injections
- pegaptanib (Macugen®) is a selective anti-VEGF targeting VEGF isoform 165 (no longer widely used)
- ranibizumab (Lucentis®) is a non-selective anti-VEGF agent
- bevacizumab (Avastin®) is another non-selective anti-VEGF agent but is only FDA approved for metastatic breast cancer, colorectal cancer and non-small cell lung cancer. Therefore, its ophthalmologic use is off-label

**TOPICAL OCULAR THERAPEUTIC DRUGS****NSAIDs**

- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

**Anti-Histamines**

- used to relieve red and itchy eye, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes

**Decongestants**

- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine (Isopto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle closure glaucoma

**Antibiotics**

- indications: bacterial conjunctivitis, keratitis, or blepharitis
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (ciprofloxacin [Ciloxan®], ofloxacin [Ocuflox®], moxifloxacin [Vigamox®], gatifloxacin [Zymar®])

**Corticosteroids**

- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®), loteprednol etabonate 0.5% (Lotamax®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  - potentiates HSV keratitis and fungal keratitis as well as masks symptoms
  - increased IOP, more rapidly in steroid responders (within weeks)
  - posterior subcapsular cataract (within months)

## References

**Books**

Bradford C. Basic ophthalmology for medical students and primary care residents, 7th ed. San Francisco: American Academy of Ophthalmology, 1999.

Wilson FM. Practical ophthalmology: a manual for beginning residents, 4th ed. American Academy of Ophthalmology, 2005.

Friedman N, Pineda R, Kaiser P. The Massachusetts eye and ear infirmary illustrated manual of ophthalmology. Toronto: WB Saunders, 1998.

Kanski JJ. Clinical Ophthalmology: A systematic approach, 6th ed. Oxford: Butterworth-Heinemann, 2007.

Stein R, Stein H. Management of ocular emergencies, 4th ed. Montreal: Mediconcept, 2006.

Tasman W, Jaeger EA. Duane's ophthalmology, 2011 ed. Philadelphia: Lippincott Williams & Wilkins, 2010.

**Images**

Atlas of ophthalmology. Available from: [www.atlasophthalmology.com/atlas/frontpage.jsf](http://www.atlasophthalmology.com/atlas/frontpage.jsf).

**Journal Articles**

Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001;119:1417-1436.

Ambati BK, Ambati J, Azar N, Stratton L, Schmidt EV. Periorbital and orbital cellulitis before and after the advent of Haemophilus influenza type B vaccination. Ophthalmol 2000;107:1450-1453.

Anderson DR. Normal Tension Glaucoma Study. Collaborative normal tension glaucoma study. Curr Opin Ophthalmol 2003;14:6-90.

Beck RW. The optic neuritis treatment trial: three-year follow-up results. Arch Ophthalmol 1995;113:136-137.

Berson EL, Rosner B, Sandberg M, Hayes C, Nicholson BW, Weigel-DiFranco C, Willett W. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. Arch Ophthalmol 1993;111:761-782.

Bhagat N, Nagori S, Zarbin M. Post-traumatic Infectious Endophthalmitis. Surv Ophthalmol 2011;56:214-51.

CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SJ, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. NEJM 2011;364:1897-1908.

Elman MJ, Bressler NM, Qin H, Beck RW, Ferris FL 3rd, Friedman SM, Glassman AR, Scott IU, Stockdale CR, Sun JK. Diabetic Retinopathy Clinical Research Network. Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. Ophthalmol 2011;118:609-614.

Endophthalmitis Vitrectomy Study Group. Results of the endophthalmitis vitrectomy study: a randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Arch Ophthalmol 1995;113:1479-1496.

Haller JA, Bandello F, Belfort R Jr, Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jacques ML, Jiao J, Li XY, Whitcup SM, OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmol 2010;117:1134-1146.

Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Ophthalmol 2002;120:1268-1279.

Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, Mills RP, CIGTS Study Group. Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. Ophthalmol 2001;108:1943-1953.

Maguire AM, High KA, Auricchio A, Wright JF, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet 2009;374:1597-1605.

Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. NEJM 2011;364:603-615.

Sheikh A, Hurwitz B. Antibiotics versus placebo for acute bacterial conjunctivitis. Cochrane DB Syst Rev 2006;2:CD001211.

Smetana GW, Shmerling RH. Does this patient have temporal arteritis? JAMA 2002;287:92-101.

The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol 1984;98:271-282.

The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. NEJM 1993;329:977-986.

Turner A, Rabiou M. Patching for corneal abrasion. Cochrane DB Syst Rev 2006;2:CD0004764.

Vass C, Him C, Sycha T, Findl O, Bauer P, Schmetterer L. Medical interventions for primary open angle glaucoma and ocular hypertension. Cochrane DB Syst Rev 2007;4:CD003167.

Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. Cochrane DB Syst Rev 2008;2:CD005139.

Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane DB Syst Rev 2010;12:CD002898.

Wong AM. New concepts concerning the neural mechanisms of amblyopia and their clinical implications. Can J Ophthalmol 2012;47:399-409.

**Lectures/Cases**

University of Michigan Kellogg Eye Centre. Available from: [www.kellogg.umich.edu/theeyeshaveit/index.html](http://www.kellogg.umich.edu/theeyeshaveit/index.html).

Jonny Elserafi, Michael Neufeld, Kajeandra Ravichandiran and David Stockton, chapter editors

Jieun Kim and Daniel Soong, associate editors

Jeff Martin, EBM editor

Dr. Paul Kuzyk, Dr. Markku T. Nousiainen and Dr. Herbert P. von Schroeder, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Hip</b> . . . . .	<b>26</b>
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	Hip Dislocation	
<b>Differential Diagnosis of Joint Pain</b> . . . . .	<b>4</b>	Hip Fracture	
<b>Fractures – General Principles</b> . . . . .	<b>5</b>	Arthritis of the Hip	
Fracture Description		Hip Dislocation after Total Hip Arthroplasty	
Management of Fractures			
Fracture Healing			
General Fracture Complications			
<b>Orthopedic X-Ray Imaging</b> . . . . .	<b>6</b>	<b>Femur</b> . . . . .	<b>28</b>
<b>Orthopedic Emergencies</b> . . . . .	<b>7</b>	Femoral Diaphysis Fracture	
Trauma Patient Work-Up		Distal Femoral Fracture	
Open Fractures			
Cauda Equina Syndrome		<b>Knee</b> . . . . .	<b>29</b>
Compartment Syndrome		Evaluation of Knee	
<b>Articular Cartilage</b> . . . . .	<b>9</b>	Cruciate Ligament Tears	
Osteomyelitis		Collateral Ligament Tears	
Septic Joint		Meniscal Tears	
<b>Shoulder</b> . . . . .	<b>10</b>	Quadriceps/Patellar Tendon Rupture	
Shoulder Dislocation		Dislocated Knee	
Rotator Cuff Disease			
Acromioclavicular Joint Pathology		<b>Patella</b> . . . . .	<b>32</b>
Clavicle Fracture		Patellar Fracture	
Frozen Shoulder		Patellar Dislocation	
<b>Humerus</b> . . . . .	<b>15</b>	Patellofemoral Syndrome	
Proximal Humeral Fracture			
Humeral Shaft Fracture		<b>Tibia</b> . . . . .	<b>34</b>
<b>Elbow</b> . . . . .	<b>16</b>	Tibial Plateau Fracture	
Supracondylar Fracture		Tibial Shaft Fracture	
Radial Head Fracture			
Olecranon Fracture		<b>Ankle</b> . . . . .	<b>35</b>
Elbow Dislocation		Evaluation of Ankle and Foot Complaints	
Epicondylitis		Ankle Fracture	
<b>Forearm</b> . . . . .	<b>18</b>	Ligamentous Injuries	
Radius and Ulna Fracture			
Monteggia Fracture		<b>Foot</b> . . . . .	<b>36</b>
Nightstick Fracture		Talar Fracture	
Galeazzi Fracture		Calcaneal Fracture	
<b>Wrist</b> . . . . .	<b>19</b>	Achilles Tendonitis	
Colles' Fracture		Achilles Tendon Rupture	
Smith's Fracture		Plantar Fasciitis (Heel Spur Syndrome)	
Complications of Wrist Fractures		Bunions (Hallux Valgus)	
Scaphoid Fracture		Metatarsal Fracture	
<b>Hand</b> . . . . .	<b>PL22</b>	<b>Pediatric Orthopedics</b> . . . . .	<b>38</b>
<b>Spine</b> . . . . .	<b>21</b>	Fractures in Children	
Fractures of the Spine		Stress Fractures	
Cervical Spine		Evaluation of the Limping Child	
Thoracolumbar Spine		Epiphyseal Injury	
<b>Pelvis</b> . . . . .	<b>25</b>	Slipped Capital Femoral Epiphysis	
Pelvic Fracture		Developmental Dysplasia of the Hip	
		Legg-Calvé-Perthes Disease (Coxa Plana)	
		Osgood-Schlatter Disease	
		Congenital Talipes Equinovarus (Club Foot)	
		Scoliosis	
		<b>Bone Tumours</b> . . . . .	<b>42</b>
		Benign Active Bone Tumours	
		Benign Aggressive Bone Tumours	
		Malignant Bone Tumours	
		<b>Common Medications</b> . . . . .	<b>45</b>
		<b>References</b> . . . . .	<b>46</b>

## Acronyms

AC	acromioclavicular	FOOSH	fall on outstretched hand	OA	osteoarthritis
ACL	anterior cruciate ligament	GA	general anesthetic	ORIF	open reduction internal fixation
AIN	anterior interosseous nerve	HO	heterotopic ossification	PCL	posterior cruciate ligament
ARDS	acute respiratory distress syndrome	I&D	incision and drainage	PE	pulmonary embolism
AVN	avascular necrosis	IM	intramedullary	PIN	posterior interosseous nerve
CA	coracoacromial	LCL	lateral collateral ligament	RA	rheumatoid arthritis
CC	coracoclavicular	MCL	medial collateral ligament	ROM	range of motion
CRPS	complex regional pain syndrome	MT	metatarsal	RSD	reflex sympathetic dystrophy
DDH	developmental dysplasia of the hip	MTP	metatarso phalangeal	SCFE	slipped capital femoral epiphysis
DRUJ	distal radioulnar joint	MVC	motor vehicle collision	SLAP	superior lateral, anterior posterior
DVT	deep vein thrombosis	NVS	neurovascular status	SN	sensitivity
EtOH	ethanol/alcohol	NWB	non-weight bearing	THA	total hip arthroplasty

## Basic Anatomy Review

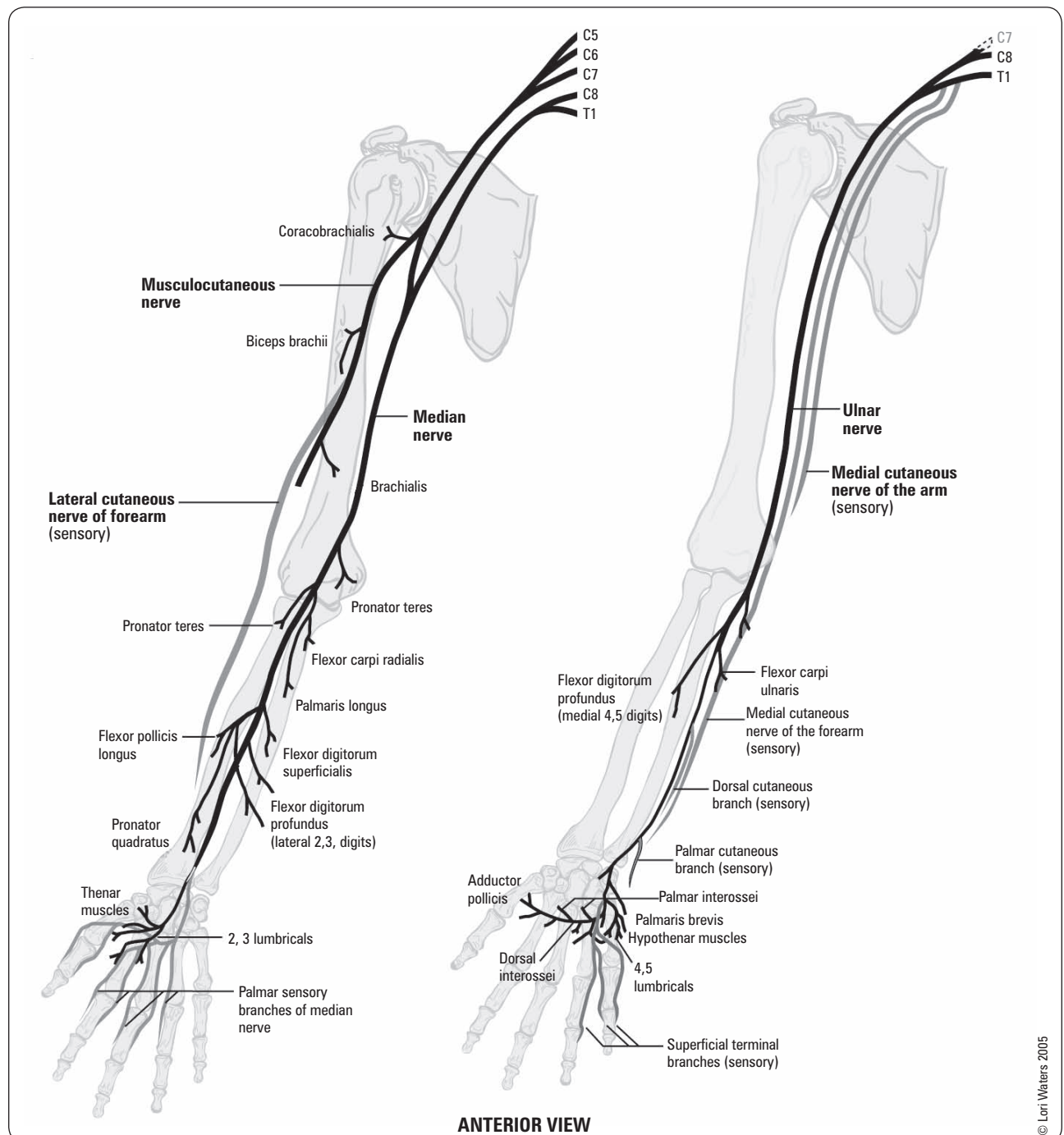
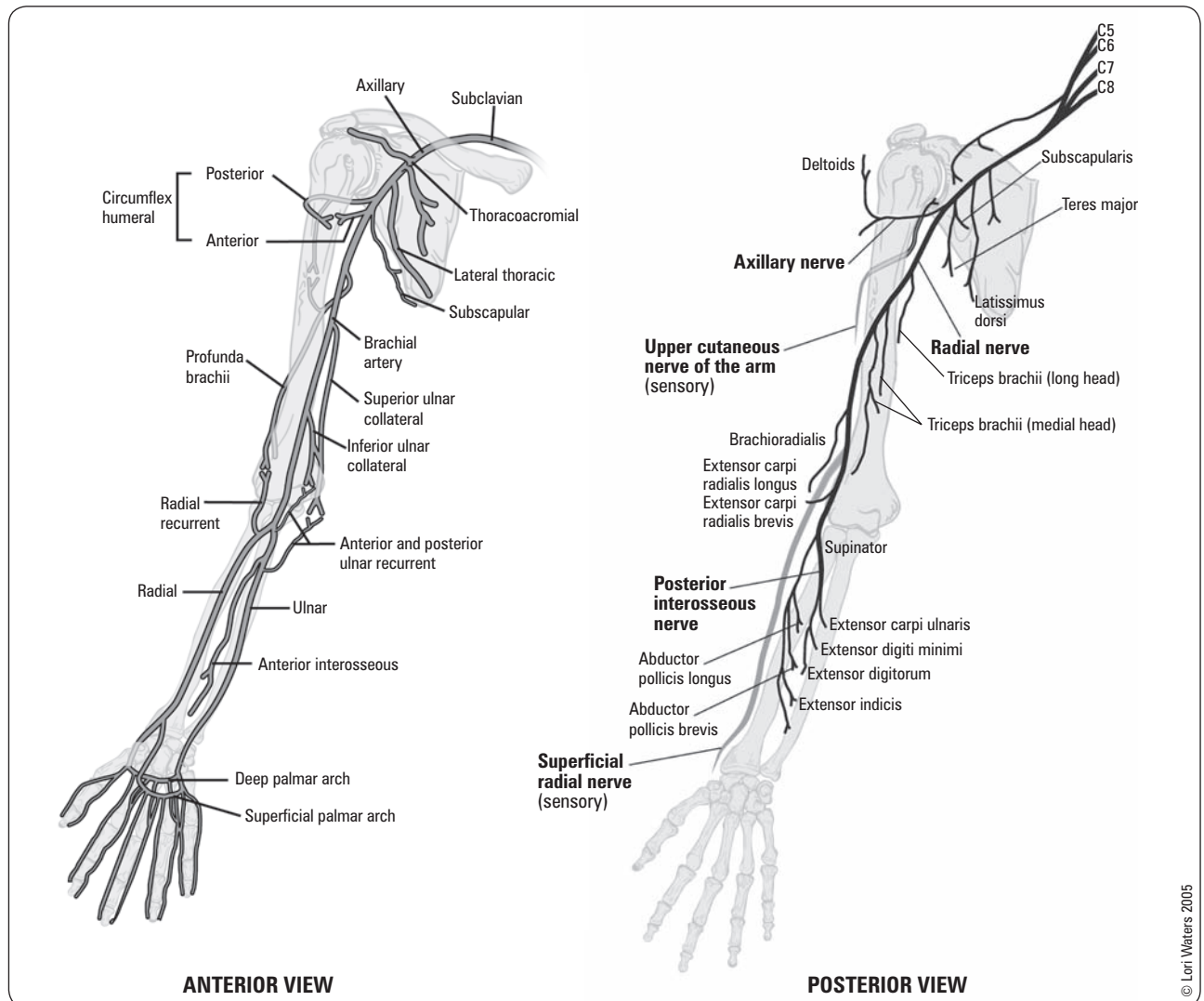


Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles





**Figure 2. (Left) Blood supply to the upper limb  
(Right) Axillary and radial nerves: innervation of the upper limb**

**Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities**

Nerve	Motor	Sensory	Nerve Roots
<b>Axillary</b>	Deltoid/Teres Minor	Lateral Upper Arm (Sergeant's Patch)	C5, C6
<b>Musculocutaneous</b>	Biceps/Brachialis	Lateral Forearm	C5, C6
<b>Radial</b>	Triceps Wrist/Thumb/Finger Extensors	Lateral Dorsum of the Hand Medial Upper Forearm	C5, C6, C7, C8
<b>Median</b>	Wrist Flexors and Abductors Flexion of the 1 <sup>st</sup> -3 <sup>rd</sup> Digits	Volar Thumb to Radial ½ of Ring Finger	C6, C7
<b>Ulnar</b>	Wrist Flexors and Adductors Flexion of the 4 <sup>th</sup> -5 <sup>th</sup> Digits	Medial Forearm Medial Dorsum and Volar of Hand (Ulnar ½ of Ring and 5 <sup>th</sup> Digit)	C8, T1
<b>Tibial</b>	Ankle Plantar Flexion Knee Flexion Great Toe Flexion	Sole of Foot	L5, S1
<b>Superficial Peroneal</b>	Ankle Eversion	Dorsum of Foot	L5, S1
<b>Deep Peroneal</b>	Ankle Dorsiflexion and Inversion Great Toe Extension	1 <sup>st</sup> Web Space	L5, S1
<b>Sural</b>		Lateral Foot	S1, S2
<b>Saphenous</b>		Anteromedial Ankle	L3, L4

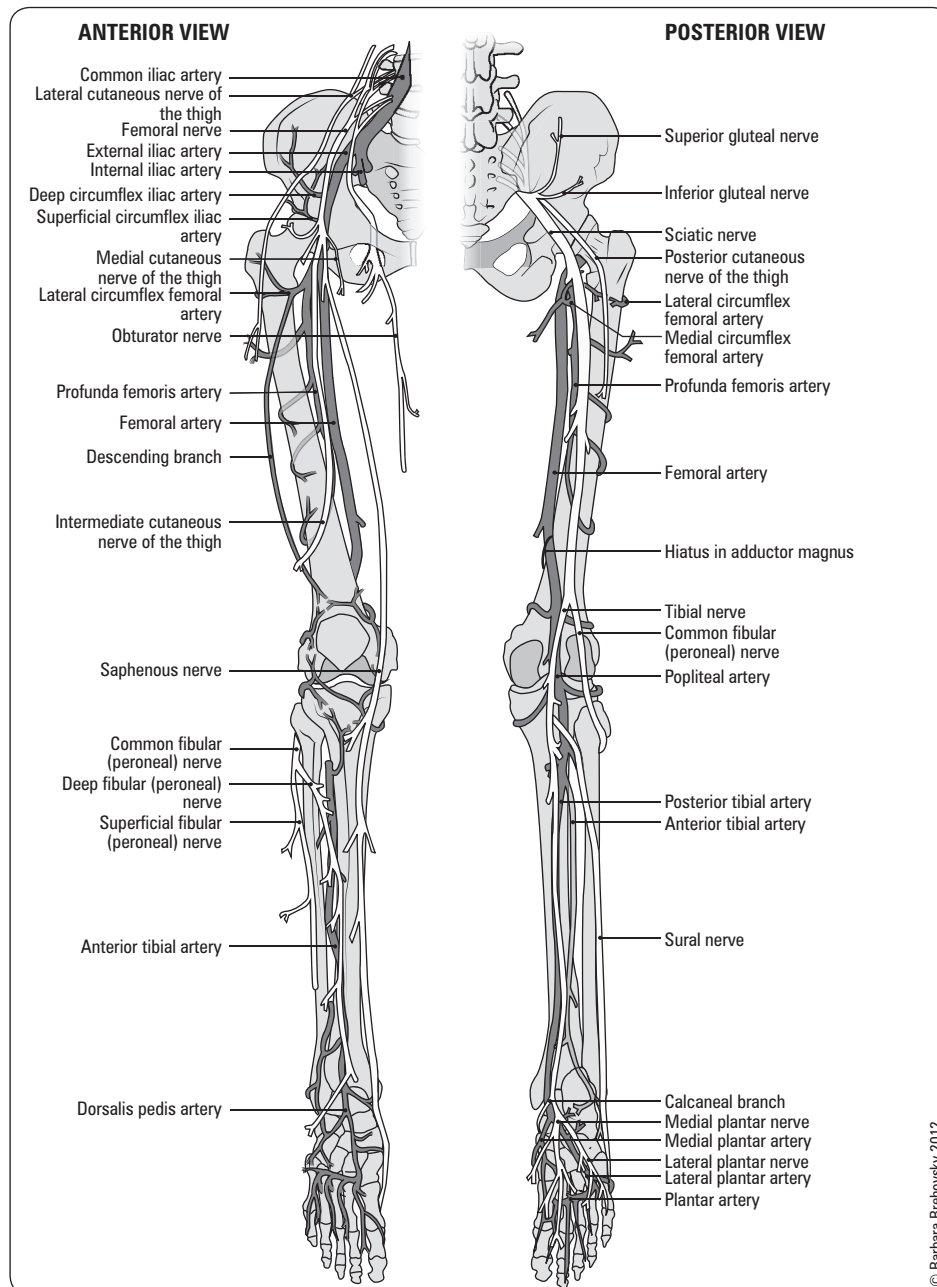


Figure 3. Nerves and arteries of lower limbs

## Differential Diagnosis of Joint Pain

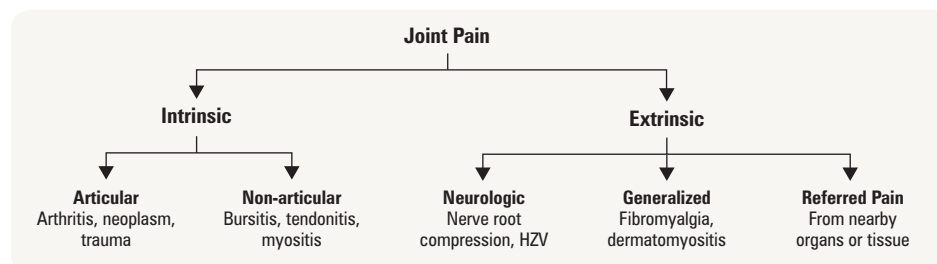


Figure 4. Intrinsic vs. extrinsic joint pain

# Fractures – General Principles



## Fracture Description

### 1. Integrity of Skin/Soft Tissue

- closed: skin/soft tissue over and near fracture is intact
- open: skin/soft tissue over and near fracture is lacerated or abraded, fracture exposed to outside environment
  - signs: continuous bleeding from puncture site or fat droplets in blood are suggestive of an open fracture

### 2. Location (Figure 5)

- epiphyseal: end of bone, forming part of the adjacent joint
- metaphyseal: the flared portion of the bone at the ends of the shaft
- diaphyseal: the shaft of a long bone (proximal, middle, distal)
- physis: growth plate

### 3. Orientation/Fracture Pattern (Figure 6)

- transverse: fracture line perpendicular to long axis of bone; direct high energy force
- oblique: angular fracture line; angular or rotational force
- butterfly: fracture site fragment which looks like a butterfly
- segmental: a separate segment of bone bordered by fracture lines; high energy
- spiral: complex, multi-planar fracture line; rotational force, low energy
- comminuted/multi-fragmentary: more than 2 fracture fragments
- intra-articular: fracture line crosses articular cartilage and enters joint
- avulsion: tendon or ligament tears/pulls fragment off bone; often in children, high energy
- compression/impacted: impaction of bone, e.g. vertebrae, proximal tibia
- torus: a buckle fracture of one cortex, often in children (Figure 51, OR38)
- green-stick: an incomplete fracture of one cortex, often in children (Figure 51, OR38)
- pathologic: fracture through bone weakened by disease/tumour

### 4. Displacement (Figure 6)

- nondisplaced: fracture fragments are in anatomic alignment
- displaced: fracture fragments are not in anatomic alignment
- distracted: fracture fragments are separated by a gap
- angulated: direction of fracture apex, e.g. varus/valgus
- translated: percentage of overlapping bone at fracture site
- rotated: fracture fragment rotated about long axis of bone

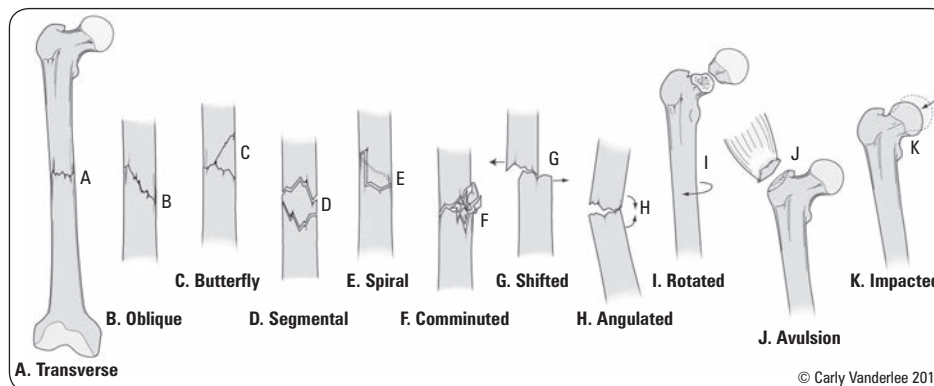


Figure 6. Fracture types

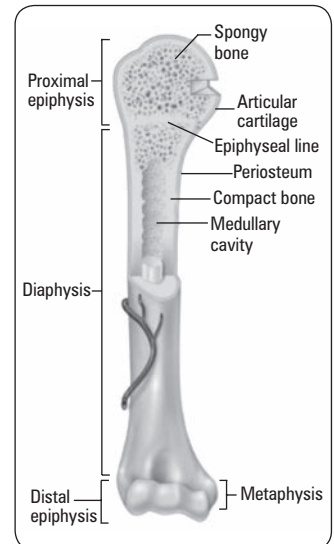


Figure 5. Schematic diagram of the long bone



#### X-Ray Rule of 2s

- 2 sides = bilateral
- 2 views = AP + lateral
- 2 joints = joint above + below
- 2 times = before + after reduction



#### Varus/Valgus Angulation

- Varus** = Apex away from midline
- Valgus** = Apex toward midline



#### Displacement

Refers to position of the distal fragment relative to the proximal fragment.



#### Quick Nerve Exam

- "Thumbs Up": PIN (Radial Nerve)
- "OK Sign": AIN (Median Nerve)
- "Spread Fingers": Ulnar Nerve



#### Reasons for Splinting

- Pain control
- Reduces further damage to vessels, nerves, and skin
- Decreases risk of inadvertently converting closed to open fracture
- Facilitates patient transport

## Management of Fractures

- ABCs, primary survey and secondary survey (ATLS protocol)
  - rule out other fractures/injuries
  - rule out open fracture (see sidebar on OR8)
- AMPLE history: Allergies, Medications, Past medical history, Last meal, Events surrounding injury
  - consider pathologic fracture with history of only minor trauma
- analgesia
- imaging
- splint extremity

1. obtain the reduction (refer to Table 27 for appropriate IV sedation)
  - closed reduction
    - ♦ apply traction in the long axis of the limb
    - ♦ reverse the mechanism that produced the fracture
    - ♦ reduce with IV sedation and muscle relaxation (fluoroscopy can be used if available)
  - indications for open reduction:
    - ♦ NO CAST
    - ♦ other indications include:
      - failed closed reduction
      - not able to cast or apply traction due to site (e.g. hip fracture)
      - pathologic fractures
      - potential for improved function with ORIF
  - re-check neurovascular status after reduction and obtain post-reduction x-ray
2. maintain the reduction
  - external stabilization: splints, casts, traction, external fixator
  - internal stabilization: percutaneous pinning, extramedullary fixation (screws, plates, wires), intramedullary fixation (rods)
  - follow-up: evaluate bone healing
3. rehabilitate to regain function and avoid joint stiffness



#### Indications for Open Reduction

##### NO CAST

Non-union  
Open fracture  
Neurovascular Compromise  
Intra-Articular fracture  
Salter-Harris 3,4,5  
PolyTrauma

## Fracture Healing

### Normal Healing

Weeks 0-3	Hematoma, macrophages surround fracture site
Weeks 3-6	Osteoclasts remove sharp edges, callus forms within hematoma
Weeks 6-12	Bone forms within the callus, bridging fragments
Months 6-12	Cortical gap is bridged by bone
Years 1-2	Normal architecture is achieved through remodelling

Figure 8. Stages of Bone Healing

### Evaluation of Healing: Tests of Union

- clinical: no longer tender to palpation or stressing on physical exam
- x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

## General Fracture Complications

Table 2. General Fracture Complications

	Early	Late
<b>Local</b>	Compartment syndrome Neurological injury Vascular injury Infection Implant failure Fracture blisters	Mal/non-union AVN Osteomyelitis HO Post-traumatic osteoarthritis Joint stiffness/adhesive capsulitis CRPS type I/RSD
<b>Systemic</b>	Sepsis DVT PE ARDS secondary to fat embolism Hemorrhagic shock	

## Orthopedic X-Ray Imaging

### General Principles

- x-ray 1 joint above and 1 below
- obtain at least 2 orthogonal views ± specialized views

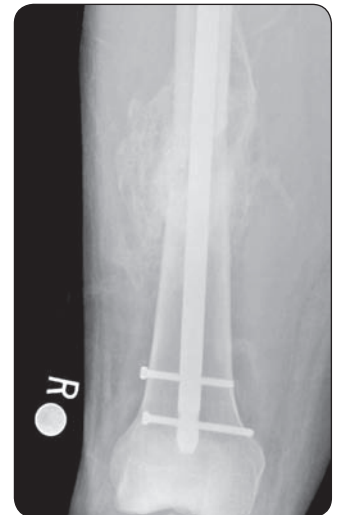


Figure 7. Heterotopic ossification of femoral diaphysis after femur fracture and intramedullary nailing



#### Heterotopic Ossification

The formation of bone in abnormal locations (e.g. in muscle), secondary to pathology.



#### Avascular Necrosis

Ischemia to bone due to disrupted blood supply; commonly in bones covered by cartilage or with distal to proximal blood supply.



#### Fracture Blister

Formation of vesicles or bullae that occur on edematous skin overlying a fractured bone.



#### CRPS/RSD

An exaggerated response to an insult in the extremities; characterized by symptoms of hyperalgesia and allodynia, with signs of autonomic dysfunction (temperature asymmetry, mottling, hair or nail changes).

**Table 3. Orthopedic X-Ray Imaging**

Site	Injury	X-Ray views
Shoulder	Anterior dislocation	AP
	Posterior dislocation	Axillary ± stress view with 10lb in hand
	Acromioclavicular	Trans-scapular
	Frozen shoulder	Zanca view (10-15 cephalic tilt)
Arm	Humerus #	AP
		Lateral
		Trans-scapular
		Axillary
Elbow/Forearm	Supracondylar #	AP
	Radial head #	Lateral
	Monteggia #	
	Night stick #	
	Galeazzi #	
Wrist	Colles' #	AP
	Smith #	Lateral
	Scaphoid #	Scaphoid (wrist extension and ulnar deviation x 2wk)
Pelvis	Pelvic #	AP pelvis
		Inlet and outlet views
		Judet views (obturator and iliac oblique for acetabular fracture)
Hip	Femoral head/neck #	AP
	Intertrochanteric #	Lateral
	Arthritis	Frog-leg
	SCFE	
Knee	Knee Dislocation	AP standing, lateral
	Femur/tibia #	Skyline – tangential view with knees flexed at 45° to see patellofemoral joint
	Patella #	
	Patella dislocation	
	Patella femoral syndrome	
	Tibia shaft #	
Ankle	Ankle #	AP
		Lateral
		Mortise view: ankle at 15° of internal rotation
Foot	Talar #	AP
	Calcaneal #	Lateral
Spine	Compression #	AP spine
	Burst #	AP odontoid
	Cervical spine #	Lateral
		Oblique
		Swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
		Lateral flexion/extension view: evaluate subluxation of cervical vertebrae

## Orthopedic Emergencies

### Trauma Patient Work-Up

#### Etiology

- high energy trauma e.g. motor vehicle accident, fall from height
- may be associated with spinal injuries or life-threatening visceral injuries

#### Clinical Presentation

- local swelling, tenderness, deformity of the limbs, and instability of the pelvis or spine
- decreased level of consciousness, hypotension/hypovolemia
- consider involvement of alcohol or other substances

#### Investigations

- trauma survey (see [Emergency Medicine](#), ER2)
- x-rays: lateral cervical spine, AP chest, AP pelvis, AP and lateral of all bones suspected to be injured
- other views of pelvis: AP, inlet and outlet; Judet views for acetabular fracture (see Table 18 for classification of pelvic fractures)



#### Orthopedic Emergencies

##### VON CHOP

- Vascular compromise
- Open fracture
- Neurological compromise/cauda equina syndrome
- Compartment syndrome
- Hip dislocation
- Osteomyelitis/septic arthritis
- Unstable Pelvic fracture



#### Buck's Traction

A system of weights, pulleys, and ropes that are attached to the end of a patient's bed exerting a longitudinal force on the distal end of a fracture, improving its length, alignment, and rotation.

### Treatment

- ABCDEs and initiate resuscitation for life threatening injuries
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- DVT prophylaxis

### Complications

- **hemorrhage – life threatening** (may produce signs and symptoms of hypovolemic shock)
- fat embolism syndrome (SOB, hypoxemia, petechial rash, thrombocytopenia and neurological symptoms)
- venous thrombosis – DVT and PE
- bladder/bowel injury
- neurological damage
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic osteoarthritis of joints with intra-articular fractures
- sepsis if missed open fracture

## Open Fractures

### Definition

- fractured bone and hematoma in communication with the external environment

### Emergency Measures

- removal of obvious foreign material
- irrigate with normal saline if grossly contaminated
- cover wound with sterile dressings
- immediate IV antibiotics (see Table 4)
- tetanus toxoid or immunoglobulin as needed
- reduce and splint fracture
- NPO and prepare for OR (bloodwork, consent, ECG, CXR)
  - operative irrigation and debridement within 6-8 h to decrease risk of infection
  - traumatic wound often left open to drain but vacuum-assisted closure dressing may be used
  - re-examine with repeat I&D in 48 h

**Table 4. Gustilo Classification of Open Fractures**

Gustilo Grade	Length of Open Wound	Description	Prophylactic Antibiotic Regimen
I	<1 cm	Minimal contamination and soft tissue injury Simple or minimally comminuted fracture	First generation cephalosporin (cefazolin) for 3 d If allergy use fluoroquinolone If MRSA +ve use vancomycin
II	1-10 cm	Moderate contamination Soft tissue injury	First generation cephalosporin (cefazolin) for 3 d plus Gram-negative coverage (gentamicin) for at least 3 d
III*	>10 cm	IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound IIIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound IIIC: Vascular injury/compromise	As per Grade II For soil contamination, penicillin is added for clostridial coverage

\*Any high energy, comminuted fracture, shot gun, farmyard/soil/water contamination, exposure to oral flora, or fracture more than 8 h old is immediately classified as Grade III



33% of patients with open fractures have multiple injuries.



### Antibiotics for Preventing Infection in Open Limb Fractures

*Cochrane DB Syst Rev 2004;1:CD003764*

**Purpose:** To review the evidence regarding the effectiveness of antibiotics in the initial treatment of open fractures of the limbs.

**Methods:** Randomized or quasi randomized controlled trials comparing antibiotic treatment with placebo or no treatment in preventing acute wound infection were identified and reviewed. Data were extracted and pooled for analysis.

**Results:** Eight studies (n=1106) were reviewed. The use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo (RRR=0.43, 95% CI: 0.29, 0.65; ARR=0.07, 95% CI: 0.03=0.10).

**Conclusions:** Antibiotics reduce the incidence of early infections in open fractures of the limbs.

## Cauda Equina Syndrome

- see [Neurosurgery](#), NS26



Cauda equina syndrome is a surgical emergency.

## Compartment Syndrome

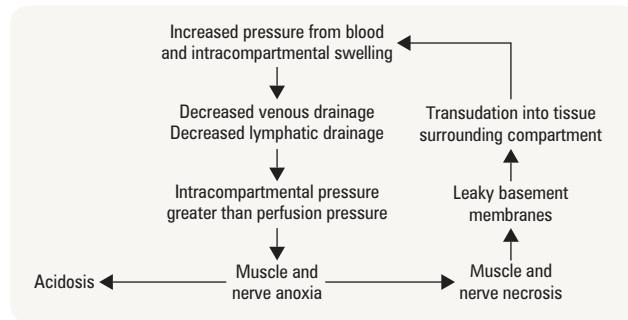
### Definition

- increased interstitial pressure in an anatomical compartment (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment) with little room for expansion
- interstitial pressure exceeds capillary perfusion pressure leading to muscle necrosis (in 4-6 h) and eventually nerve necrosis

### Etiology

- intracompartmental: fracture (particularly tibial shaft fractures, pediatric supracondylar fractures, and forearm fractures), crush injury, ischemia-reperfusion injury
- extracompartmental: constrictive dressing (circumferential cast, poor positioning during surgery), circumferential burn





**Figure 9. Pathogenesis of compartment syndrome**

### Clinical Features

- pain with active contraction of compartment
- pain with passive stretch
- swollen, tense compartment
- suspicious history
- **5 Ps:** late sign (see sidebar) – do not wait for these to develop to make the diagnosis!

### Investigations

- usually not necessary as compartment syndrome is a clinical diagnosis
- in children or unconscious patients where clinical exam is unreliable, compartment pressure monitoring with catheter AFTER clinical diagnosis is made (normal = 0 mmHg; elevated  $\geq 30$  mmHg or  $\leq 30$  mmHg of diastolic BP)

### Treatment

- non-operative
  - remove constrictive dressings (casts, splints), elevate limb at the level of the heart
- operative
  - urgent fasciotomy
  - 48-72 h post-op: wound closure  $\pm$  necrotic tissue debridement

### Complications

- rhabdomyolysis, renal failure secondary to myoglobinuria
- Volkmann's ischemic contracture: ischemic necrosis of muscle, followed by secondary fibrosis and finally calcification; especially following supracondylar fracture of humerus



#### 5 Ps of Compartment Syndrome

**Pain:** out of proportion for injury and not relieved by analgesics

- Increased pain with passive stretch of compartment muscles (most specific sign)

**Pallor:** late finding

**Paresthesia**

**Paralysis:** late finding

**Pulselessness:** late finding



Most important sign is increased pain with passive stretch. Most important symptom is pain out of proportion to injury.



Rapid progression of signs and symptoms (over hours) necessitates need for serial examinations.

## Articular Cartilage

### Properties

- 2-4 mm layer covering ends of articulating bones, provides nearly frictionless surface
- avascular (nutrition from synovial fluid), aneural, alymphatic
- composed of: collagen (90% is type II; gives tensile strength), water, proteoglycans (gives compressive strength), and chondrocytes

### ARTICULAR CARTILAGE DEFECTS

#### Etiology

- overt trauma, repetitive minor trauma (such as patellar maltracking); common sports injury
- degenerative conditions such as early stage osteoarthritis or osteochondritis dissecans

#### Clinical Features

- similar to symptoms of osteoarthritis (joint line pain with possible effusion, etc.)
- often have predisposing factors, such as ligament injury, malalignment of the joint (varus/valgus), obesity, bone deficiency (avascular necrosis, osteochondritis dissecans, ganglion bone cysts), inflammatory arthropathy, and familial osteoarthropathy
- may have symptoms of locking or catching related to the torn/displaced cartilage

#### Investigations

- x-ray (to rule out bony defects and check alignment)
- MRI
- diagnostic arthroscopy (treatment is often guided by what is seen during arthroscopy)

**Table 5. Outerbridge Classification of Chondral Defects**

Grade	Chondral Damage
I	Softening and swelling of cartilage
II	Fragmentation and fissuring <1/2 inch in diameter
III	Fragmentation and fissuring >1/2 inch in diameter
IV	Erosion of cartilage down to bone

**Treatment**

- individualized; must take into account patient factors (age, skeletal maturity, activity level, etc.) and defect factors (Outerbridge classification, subchondral bone involvement, etc.)
- non-operative: rest, NSAIDs, bracing
- operative: microfracture, osteochondral grafting (autograft or allograft), autologous chondrocyte implantation

**Osteomyelitis****Treatment**

Acute Osteomyelitis	Chronic Osteomyelitis
IV antibiotics; started empirically and adjusted after obtaining blood and aspirate cultures ± surgery for abscess	Surgical debridement Antibiotics: both local (e.g. antibiotic beads) and systemic (IV)

**Plain Film Findings of Osteomyelitis**

- Soft tissue swelling
- Lytic bone destruction\*
- Periosteal reaction (formation of new bone, especially in response to #)\*

\*Generally not seen on plain films until 10-12 d after onset of infection.

**Septic Joint****Etiology**

- most commonly caused by *Staphylococcus aureus* in adults
- consider coagulase-negative *Staphylococcus* in patients with prior joint replacement
- consider *Neisseria gonorrhoeae* in sexually active adults
- most common route of infection is hematogenous
- risk factors: age >80 yr, DM, RA, prosthetic joint, recent joint surgery, skin infection/ulcer, IV drug use, alcoholism, previous intra-articular corticosteroid injection

**Clinical Presentation**

- inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling, pain on active and passive ROM, ± fever

**Investigations**

- x-ray (to r/o fracture, tumour, metabolic bone disease), ESR, CRP, WBC, blood cultures
- joint aspirate: WBC >80,000 with >90% neutrophils, protein level >4.4 mg/dL, joint glucose level << blood glucose level, no crystals, positive Gram stain results
- listen for heart murmur (to r/o infective endocarditis)

**Treatment**

- IV antibiotics, empiric therapy (based on age and risk factors), adjust following joint aspirate C&S results
- for small joints: needle aspiration, serial if necessary until sterile
- for major joints such as knee, hip, or shoulder: urgent decompression and surgical drainage



Acute osteomyelitis is a medical emergency which requires an early diagnosis and appropriate antimicrobial and surgical treatment.

**Plain Film Findings in a Septic Joint**

- Early (0-3 d): usually normal  
May show soft-tissue swelling or joint space widening from localized edema
- Late (4-6 d): joint space narrowing and destruction of cartilage



Serial C-reactive protein (CRP) can be used to monitor response to therapy.

**Shoulder****Shoulder Dislocation****Prognosis**

- recurrence rate depends on age of 1st dislocation: <20 yr = 65-95%; 20-40 yr = 60-70%; >40 yr = 2-4%

**Specific Complications**

- rotator cuff or capsular tear, shoulder stiffness
- injury to axillary nerve/artery, brachial plexus
- recurrent/unreduced dislocation (most common complication)

**Investigations**

- anterior dislocation x-rays (AP, trans-scapular, axillary views)
- posterior dislocation x-rays (AP, trans-scapular, axillary) or CT scan



**There are 4 Joints in the Shoulder:**  
glenohumeral, acromioclavicular (AC), sternoclavicular (SC), scapulothoracic.

Shoulder passive ROM: abduction – 180°, adduction – 45°, flexion – 180°, extension – 45°, int. rotation – level of T4, ext. rotation – 40-45°.

Table 6. Anterior and Posterior Shoulder Dislocation

	Anterior Shoulder Dislocation (>90%)	Posterior Shoulder Dislocation (5%)
<b>MECHANISM</b>	Abducted arm is externally rotated/hyperextended, or blow to posterior shoulder Involuntary, usually traumatic; voluntary, atraumatic	Adducted, internally rotated, flexed arm FOOSH 3 Es (epileptic seizure, EtOH, electrocution) Blow to anterior shoulder
<b>CLINICAL FEATURES</b>		
<b>Symptoms</b>	Pain, arm slightly abducted and externally rotated with inability to internally rotate	Pain, arm is held in adduction and internal rotation; external rotation is blocked
<b>Shoulder Exam</b>	<p>"Squared off" shoulder</p> <p>+ve apprehension test: patient looks apprehensive with gentle shoulder abduction and external rotation to 90° since humeral head is pushed anteriorly and recreates feeling of anterior dislocation (Figure 13)</p> <p>+ve relocation test: a posteriorly directed force applied during the apprehension test relieves apprehension since anterior subluxation is prevented</p> <p>+ve sulcus sign: presence of subacromial indentation with distal traction on humerus indicates inferior shoulder instability (Figure 13)</p>	<p>Anterior shoulder flattening, prominent coracoid, palpable mass posterior to shoulder</p> <p>+ve posterior apprehension ("jerk") test: with patient supine, flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will "jerk" back with the sensation of subluxation (Figure 13)</p> <p>Note: the posterior apprehension test is used to test for recurrent posterior instability, NOT for acute injury</p>
<b>Neurovascular Exam Including</b>	<p>Axillary nerve: sensory patch over deltoid and deltoid contraction</p> <p>Musculocutaneous nerve: sensory patch on lateral forearm and biceps contraction</p>	Full neurovascular exam as per anterior shoulder dislocation
<b>RADIOGRAPHIC FINDINGS</b>		
<b>Axillary View</b>	Humeral head is anterior	Humeral head is posterior
<b>Trans-scapular 'Y' View</b>	<p>Humeral head is anterior to the centre of the "Mercedes-Benz sign" (Figure 11)</p> <p>Humeral head is posterior to centre of "Mercedes-Benz sign" (Figure 11)</p>	
<b>AP View</b>	Sub-coracoid lie of the humeral head is most common	Partial vacancy of glenoid fossa (vacant glenoid sign) and >6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign)
<b>Hill-Sachs and Bony Bankart Lesions</b>	<p>± Hill-Sachs lesion: compression fracture of posterior humeral head due to forceful impaction of an anteriorly dislocated humeral head against the glenoid rim (Figure 12)</p> <p>± bony Bankart lesion: avulsion of the anterior glenoid labrum (with attached bone fragments) from the glenoid rim (Figure 12)</p>	<p>± reverse Hill-Sachs lesion (75% of cases): divot in anterior humeral head</p> <p>± reverse bony Bankart lesion: avulsion of the posterior glenoid labrum from the bony glenoid rim</p>
<b>TREATMENT</b>	<p>Closed reduction with IV sedation and muscle relaxation</p> <p>Traction-countertraction: assistant stabilizes torso with a folded sheet wrapped across the chest while the surgeon applies gentle steady traction (Figure 13)</p> <p>Stimson: while patient lies prone with arm hanging over table edge, hang a 5 lb weight on wrist for 15-20 min</p> <p>Hippocratic method: place heel into patient's axilla and apply traction to arm</p> <p>Cunningham's method: low risk, low pain; if not successful try above methods</p> <p>Obtain post-reduction x-rays</p> <p>Check post-reduction NVS</p> <p>Sling x 3 wk (avoid abduction and ext. rotation), followed by shoulder rehabilitation (dynamic stabilizer strengthening)</p>	<p>Closed reduction with sedation and muscle relaxation</p> <p>Inferior traction on a flexed elbow with pressure on the back of the humeral head</p> <p>Obtain post-reduction x-rays</p> <p>Check post-reduction NVS</p> <p>Sling in abduction and external rotation x 3 wk, followed by shoulder rehabilitation (dynamic stabilizer strengthening)</p>

**Factors Causing Shoulder Instability**

- Shallow glenoid
- Loose capsule
- Ligamentous laxity

**Frequency of Dislocations:**

- Anterior shoulder > Posterior shoulder
- Posterior hip > Anterior hip

The glenohumeral joint is the most commonly dislocated joint in the body since stability is sacrificed for motion.

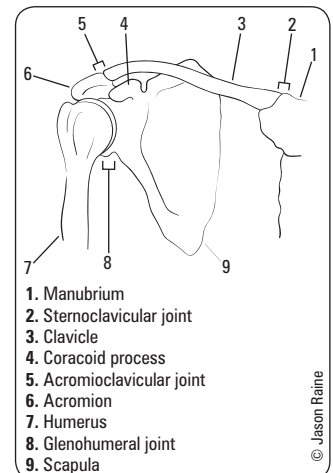


Figure 10. Shoulder joints

**Posterior Shoulder Dislocation**

Up to 60-80% of are missed on initial presentation due to poor physical exam and radiographs.

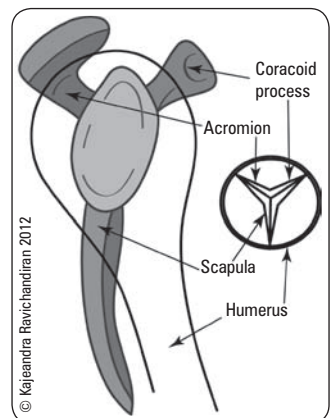


Figure 11. Mercedes-Benz

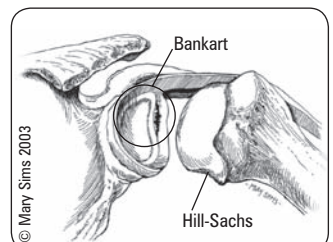


Figure 12. Posterior view of anterior dislocation causing Hill-Sachs and Bankart lesions

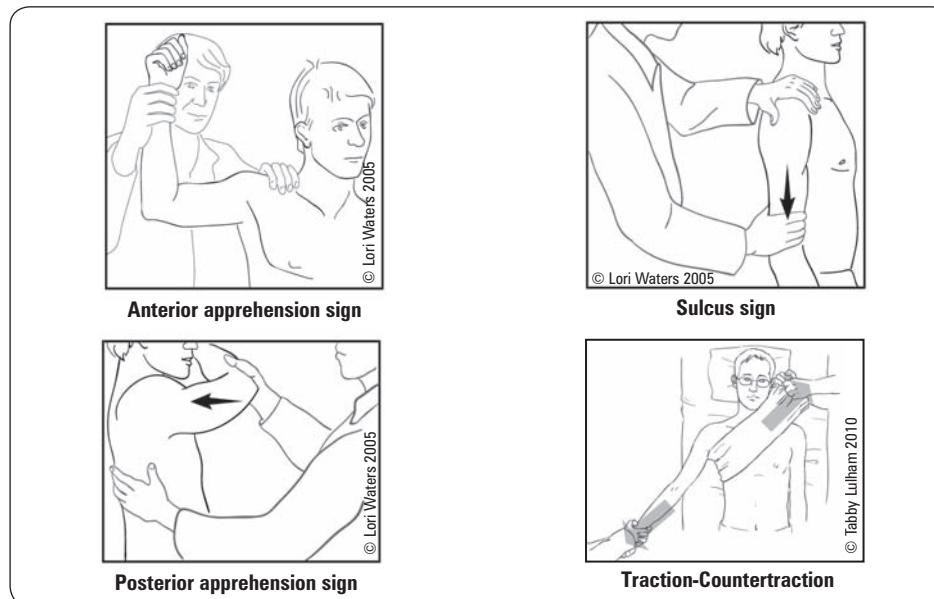


Figure 13. Shoulder maneuvers

## Rotator Cuff Disease

- rotator cuff consists of 4 muscles (Table 7) that act to stabilize humeral head within the glenoid fossa (see Figure 14)

Table 7. Rotator Cuff Muscles

Muscle	Muscle Attachments		Nerve Supply	Muscle Function
	Proximal	Distal		
<b>Supraspinatus</b>	Scapula	Greater tuberosity of humerus	Suprascapular nerve	Abduction
<b>Infraspinatus</b>	Scapula	Greater tuberosity of humerus	Suprascapular nerve	External rotation
<b>Teres Minor</b>	Scapula	Greater tuberosity of humerus	Axillary nerve	External rotation
<b>Subscapularis</b>	Scapula	Lesser tuberosity of humerus	Subscapular nerve	Internal rotation and adduction

## SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

### Etiology

- impingement: “painful arc syndrome”, compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the undersurface of acromion, AC joint and CA ligament leads to bursitis, tendonitis and if left untreated, can lead to rotator cuff thinning and tear
- anything that leads to a narrow subacromial space
  - glenohumeral muscle weakness leading to abnormal motion of humeral head
  - scapular muscle weakness leading to abnormal motion of acromion
  - acromial abnormalities such as congenital narrow space or osteophyte formation

### Clinical Features

- night pain and difficulty sleeping on affected side
- pain worse with active motion
- weakness and loss of range of motion especially between 90°-130° (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity
- rule out bicep tendinosis: Speed and Yergason's tests; SLAP lesion: O'Brien's test

Table 8. Rotator Cuff Special Tests (Figure 15)

Test	Examination	Positive Test
<b>Jobe's Test</b>	Supraspinatus: place the shoulder in 90° of abduction and 30° of forward flexion and internally rotate the arm so that the thumb is pointing toward the floor	Weakness with active resistance suggests a supraspinatus tear
<b>Lift-off Test</b>	Subscapularis: internally rotate arm so dorsal surface of hand rests on lower back. Patient instructed to actively lift hand away from back against examiner resistance. (use Belly Press Test if too painful)	Inability to actively lift hand away from back suggests a subscapularis tear

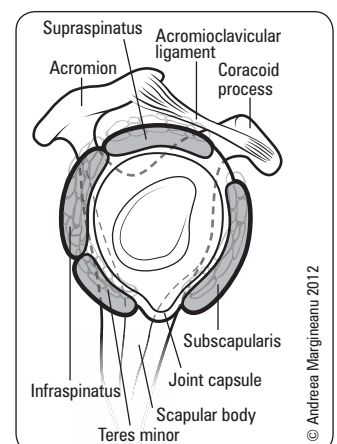


Figure 14. Muscles of the rotator cuff



### Rotator Cuff Muscles

#### SITS

Supraspinatus  
Infraspinatus  
Teres minor  
Subscapularis

**Table 8. Rotator Cuff Special Tests (Figure 15) (continued)**

Test	Examination	Positive Test
<b>Posterior-Cuff Test</b>	Infraspinatus and teres minor: arm positioned at patient's side in 90° of flexion. Patient instructed to externally rotate arm against the resistance of the examiner	Weakness with active resistance suggests posterior cuff tear
<b>Neer's Test</b>	Rotator cuff impingement: passive shoulder flexion	Pain elicited between 130-170° suggests impingement
<b>Hawkins-Kennedy Test</b>	Rotator cuff impingement: shoulder flexion to 90° and passive internal rotation	Pain with internal rotation suggests impingement
<b>Painful Arc Test</b>	Rotator cuff tendinopathy: patient instructed to actively abduct the shoulder	Pain with abduction greater than 90° suggests tendinopathy

**Screening Out Rotator Cuff Tears**

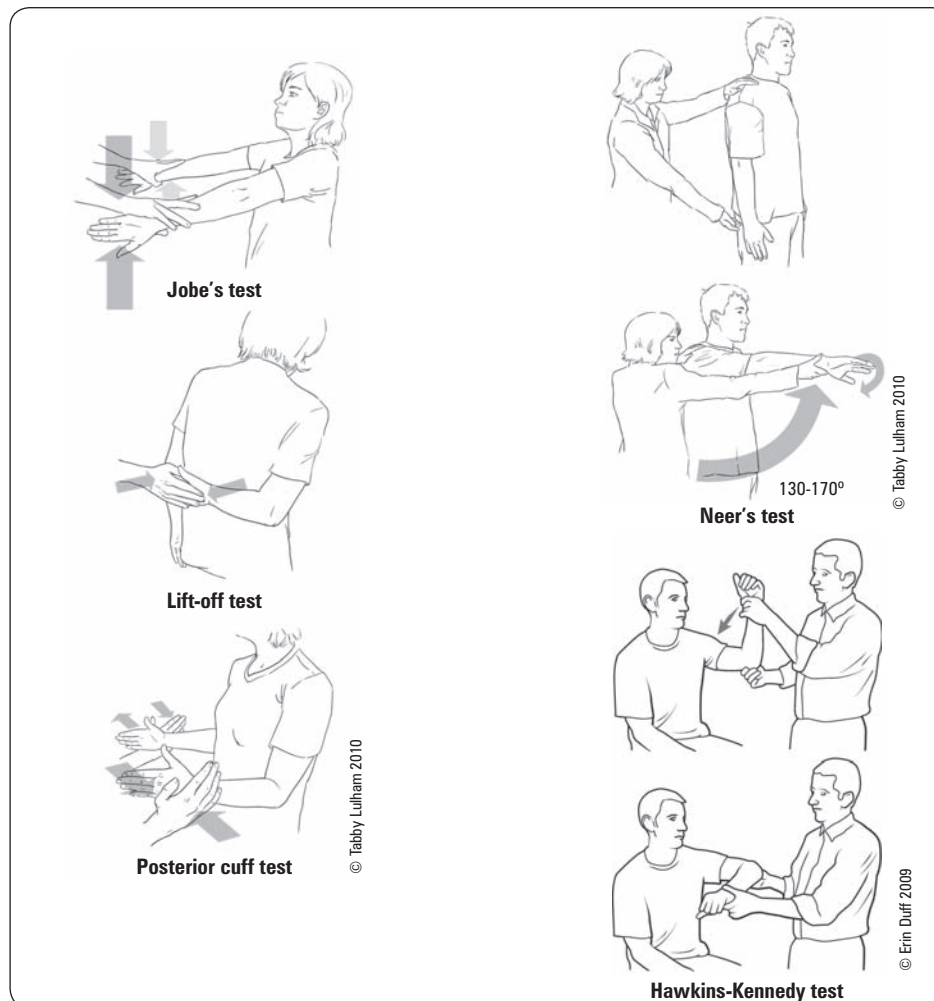
- No night pain (SN 87.7%)
- No painful arc (SN 97.5%)
- No impingement signs (SN 97.2%)
- No weakness

Returning to the bedside: Using the history and physical examination to identify rotator cuff tears. *JAM Geri Soc* 2000;48:1633-1637

**Ruling in Rotator Cuff Tears – 98% probability of rotator cuff tear if all 3 of the following are present:**

- Supraspinatus weakness
- External rotation weakness
- Positive impingement sign(s)

Diagnosis of rotator cuff tears. *Lancet* 2001; 357:769-770

**Figure 15. Rotator cuff tests****Investigations**

- x-rays: AP view may show high riding humerus relative to glenoid, evidence of chronic tendonitis
- MRI: coronal/sagittal oblique and axial orientations are useful for assessing full/partial tears and tendinopathy ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
- arthrogram: see full thickness tear, difficult to assess partial thickness tears

**Treatment and Prognosis**

- mild ("wear")
  - treatment is non-operative (physiotherapy, NSAIDs)
- moderate ("tear")
  - non-operative treatment ± steroid injection
- severe ("repair")
  - impingement that is refractory to 2-3 mo physio and 1-2 injections
  - may require arthroscopic or surgical repair, i.e. acromioplasty, rotator cuff repair



## Acromioclavicular Joint Pathology

- 2 main ligaments attach clavicle to scapula: AC and CC ligaments

### Mechanism

- fall onto shoulder with adducted arm (fall onto tip of shoulder)

### Clinical Features

- palpate step deformity between distal clavicle and acromion (with dislocation)
- pain with adduction of shoulder and/or palpation over AC joint
- limited ROM

### Investigations

- x-rays: AP, Zanca view (10-15° cephalic tilt), axillary ± stress views (10 lb weight in patient's hand)

### Treatment

- non-operative (**most common**): sling 1-3 wk, ice, analgesia, rehabilitation
- operative
  - indications: AC and CC ligaments are both torn and/or clavicle displaced posteriorly
  - procedure: excision of lateral clavicle with AC/CC ligament reconstruction



Pneumothorax or pulmonary contusion are potential complications of severe acromioclavicular joint dislocation.

**Table 9. Rockwood Classification of Acromioclavicular Joint Separation**

Grade	Features	Treatment
I	Joint sprain, absence of complete tear of either ligament	Non-operative
II	Complete tear of AC ligament, incomplete tear of CC ligament, without marked elevation of lateral clavicular head	Non-operative
III	Complete tear of AC and CC ligaments, >5 mm elevation at AC joint, superior aspect of acromion is below the inferior aspect of the clavicle	Most non-operative, operative as per indications above Will heal with step deformity, although most fully functional in 4-6 mo
IV-VI	Based on the anatomical structure the displaced clavicle is in proximity with	Operative in most cases

## Clavicle Fracture

- incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
- common in children (unites rapidly without complications)

### Mechanism

- fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

### Clinical Features

- pain and tenting of skin
- arm is clasped to chest to splint shoulder and prevent movement

### Treatment

- evaluate neurovascular status of entire upper limb
- medial and middle third clavicle fractures
  - figure-of-eight sling x 1-2 wk
  - early ROM and strengthening once pain subsides
  - if ends overlap >2 cm consider ORIF
- distal third clavicle fractures
  - undisplaced (with ligaments intact): sling x 1-2 wk
  - displaced (CC ligament injury): ORIF

### Specific Complications (see General Fracture Complications, OR6)

- cosmetic bump usually only complication
- shoulder stiffness, weakness with repetitive activity
- pneumothorax, brachial plexus injuries and subclavian vessel (all very rare)



#### Associated Injuries with Clavicle Fractures

- Up to 9% of clavicle fractures are associated with other fractures (most commonly rib fractures)
- Majority of brachial plexus injuries are associated with proximal third fractures

## Frozen Shoulder (Adhesive Capsulitis)

### Definition

- disorder characterized by progressive pain and stiffness of the shoulder usually resolving spontaneously after 18 mo



**Mechanism**

- primary adhesive capsulitis
  - idiopathic, usually associated with diabetes mellitus
  - usually resolves spontaneously in 9-18 mo
- secondary adhesive capsulitis
  - due to prolonged immobilization
  - shoulder-hand syndrome: CRPS/RSD characterized by arm and shoulder pain, decreased motion, and diffuse swelling
  - following myocardial infarction, stroke, shoulder trauma
  - poorer outcomes

**Clinical Features**

- gradual onset (weeks to months) of diffuse shoulder pain with:
  - decreased active and passive ROM
  - pain worse at night and often prevents sleeping on affected side
  - increased stiffness as pain subsides: continues for 6-12 mo after pain has disappeared

**Investigations**

- x-rays may be normal, or may show demineralization from disease

**Treatment**

- Freezing Phase
  - active and passive ROM (physiotherapy)
  - ♦ NSAIDs and steroid injections if limited by pain
- Thawing Phase
  - manipulation under anaesthesia and early physiotherapy
  - ♦ arthroscopy for debridement/decompression

**Conditions Associated with an Increased Incidence of Adhesive Capsulitis**

- Prolonged immobilization (most significant)
- Female gender
- Age > 49 yr
- Diabetes mellitus (5x)
- Cervical disc disease
- Hyperthyroidism
- Stroke
- Myocardial infarction
- Trauma and surgery



Anatomic neck fractures disrupt blood supply to the humeral head and AVN of the humeral head may ensue.

## Humerus



### Proximal Humeral Fracture

**Mechanism**

- young: high energy trauma (MVC)
- elderly: FOOSH from standing height in osteoporotic individuals

**Clinical Features**

- proximal humeral tenderness, deformity with severe fracture, swelling, painful ROM, bruising extends down arm later

**Investigations**

- test axillary nerve function (deltoid contraction and skin over deltoid)
- x-rays: AP, trans-scapular, axillary are essential
- CT scan: to evaluate for articular involvement and fracture displacement

**Classification**

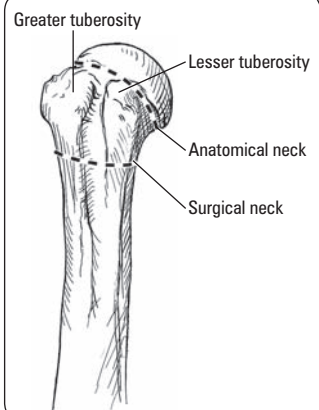
- Neer classification is based on 4 fracture fragments (see *Neer Classification* sidebar)
- displaced: displacement >1 cm and/or angulation >45°
- the Neer system regards displacement, not the fracture line, as meeting criteria for a 'part' in the classification scheme
- ± dislocated/subluxed: humeral head dislocated/subluxed from glenoid

**Treatment**

- treat osteoporosis if needed
- non-operative (nondisplaced or minimally displaced)
  - broad arm sling immobilization (nondisplaced): begin ROM in 7-10 d to prevent stiffness
  - closed reduction (minimally displaced) with sling immobilization x 2 wk, gentle ROM
- operative
  - ORIF (anatomic neck fractures, displaced, associated dislocated glenohumeral joint)
  - hemiarthroplasty may be necessary, especially in elderly

**Specific Complications** (see *General Fracture Complications*, OR6)

- AVN, axillary nerve palsy, malunion, post-traumatic arthritis



**Figure 16. Fractures of the proximal humerus**

**Neer Classification****Based on 4 parts of humerus**

- Greater Tuberosity
- Lesser Tuberosity
- Humeral Head
- Shaft

**Two-part fracture:** any of the 4 parts with 1 displaced

**Three-part fracture:** displaced fracture of surgical neck + displaced greater tuberosity or lesser tuberosity

**Four-part fracture:** displaced fracture of surgical neck + both tuberosities



70-80% of proximal humeral fractures are non-displaced and managed non-operatively. Of displaced fractures, 20% are two-part, 5% are three-part, and <1% are four-part.

## Humeral Shaft Fracture

### Mechanism

- direct blows/MVC (most common), FOOSH, twisting injuries, metastases (in elderly)

### Clinical Features

- pain, swelling,  $\pm$  shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment: look for drop wrist, sensory impairment dorsum of hand

### Investigations

- x-rays: AP and lateral radiographs of the humerus including the shoulder and elbow joints

### Treatment

- in general, humeral shaft fractures are treated non-operatively
- non-operative (**most common**)
  - $\pm$  reduction; can accept deformity due to compensatory range of motion of shoulder
  - hanging cast (weight of arm in cast provides traction across fracture site) with collar and cuff sling immobilization until swelling subsides, then Sarmiento functional brace, followed by ROM
- operative
  - indications: open fracture, neurovascular injury, unacceptable fracture alignment, polytrauma, segmental fracture, pathological fracture, "floating elbow" (simultaneous unstable humeral and forearm fractures), intra-articular
  - ORIF: plating (most common), intramedullary rod insertion, external fixation

### Specific Complications (see General Fracture Complications, OR6)

- radial nerve palsy: expect spontaneous recovery in 3-4 mo, otherwise send for EMG
- non-union: most frequently seen in middle 1/3
- decreased ROM
- compartment syndrome



#### Acceptable Humeral Shaft Deformities for Non-operative Treatment

- $<20^\circ$  anterior angulation
- $<30^\circ$  varus angulation
- $<3$  cm of shortening



Risk of radial nerve and brachial artery injury!

## Elbow



## Supracondylar Fracture

- most common in pediatric population (peak age  $\sim 7$  yr old), rarely seen in adults
- fracture of the distal 1/3 of humerus just proximal to capitulum and trochlea, usually transverse
- AIN injury commonly associated with extension type

### Mechanism

- $>96\%$  are extension injuries via FOOSH (e.g. fall off monkey bars);  $<4\%$  are flexion injuries

### Clinical Features

- pain, swelling, point tenderness
- neurovascular injury: assess median and radial nerve, radial artery (check radial pulse)

### Investigations

- x-rays: AP, lateral of elbow (Figure 17)
- assess for anterior fat pad ('sail sign') or the presence of a posterior fat pad representative of an occult fracture (Figure 18)

### Treatment

- reduction indications: evidence of arterial obstruction, unacceptable angulation, displaced ( $>50\%$ )
- non-operative
  - nondisplaced: long arm plaster slab in  $90^\circ$  flexion x 3 wk
- operative
  - indications: displaced, vascular injury, open fracture
  - requires percutaneous pinning followed by limb cast with elbow flexed  $>90^\circ$
  - in adults, ORIF is necessary

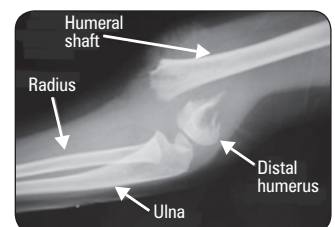
### Specific Complications (see General Fracture Complications, OR6)

- stiffness is most common
- brachial artery injury (kinking can occur if displaced fracture), median or ulnar nerve injury, compartment syndrome (leads to Volkmann's ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)



#### Three Joints at the Elbow

- Humero-radial joint
- Humero-ulnar joint
- Radioulnar joint



**Figure 17. X-ray of transverse displaced supracondylar fracture of humerus with elbow dislocation**



Normal carrying angle of elbow is approximately  $10^\circ$  of valgus.

## Radial Head Fracture

- a common fracture of the upper limb in young adults

### Mechanism

- FOOSH with elbow extended and forearm pronated

### Clinical Features

- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, mechanical block to forearm pronation and supination
- pain on pronation/supination

### Investigations

- x-ray: enlarged anterior fat pad ("sail sign") or the presence of a posterior fat pad indicates occult radial head fractures (Figure 18)

**Table 10. Classification and Treatment of Radial Head Fractures**

Mason Class	Radiographic Description	Treatment
1	Undisplaced fracture	Elbow slab or sling x 3-5 d with early ROM
2	Displaced fracture	ORIF if: angulation >30°; involves ≥1/3 of the radial head, or if ≥3 mm of joint incongruity exists
3	Comminuted fracture	Radial head excision ± prosthesis
4	Comminuted fracture with posterior elbow dislocation	Radial head excision ± prosthesis

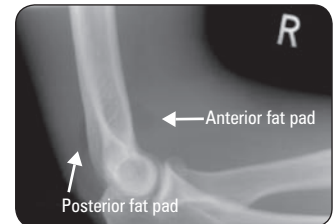
### Specific Complications (see *General Fracture Complications*, OR6)

- myositis ossificans
- recurrent instability (if medial collateral ligament injured and radial head excised)



#### Terrible Triad

- Radial head fracture
- Coronoid fracture
- Elbow dislocation



**Figure 18. X-ray of fat pad sign**

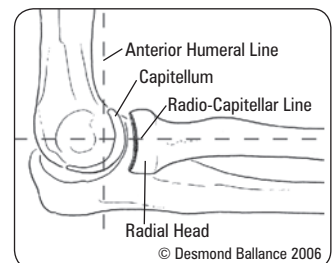


#### Mason Class 2 Radial Head Fracture

CT reconstruction provides the best detail and ability to appreciate the anatomic orientation of the fracture pattern, enhancing surgical planning and prognosis.



To avoid stiffness do not immobilize elbow joint >2-3 wk.



**Figure 19. Lateral view of elbow**



#### Elbow Dislocation

The radio-capitellar line refers to an imaginary line along the longitudinal axis of the radius that passes through the centre of the capitellum regardless of the degree of elbow flexion. If the radio-capitellar line does not pass through the centre of the capitellum a dislocation should be suspected.



The anterior humeral line refers to an imaginary line drawn along the anterior surface of the humeral cortex that passes through the middle third of the capitellum when extended inferiorly. In subtle supracondylar fractures the anterior humeral line is disrupted, typically passing through the anterior third of the capitellum.

## Olecranon Fracture

### Mechanism

- direct trauma to posterior aspect of elbow (fall onto the point of the elbow)

### Clinical Features

- ± loss of active extension due to avulsion of triceps tendon

### Treatment

- undisplaced (<2 mm, stable): cast x 10-14 d (elbow in 90° flexion) then gentle ROM
- displaced: ORIF (plate and screws or tension band wiring) and early ROM if stable

## Elbow Dislocation

- third most common joint dislocation after shoulder and patella
- usually the radius and ulna are dislocated together, or the radius head dislocates and the ulna remains ("Monteggia")
- anterior capsule and collateral ligaments disrupted

### Mechanism

- elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion
- most commonly occurs in young people (5-25 yr) in sporting events or high speed MVCs
- 90% are posterior/posterolateral, anterior are rare and usually devastating

### Clinical Features

- elbow pain, swelling, deformity
- flexion contracture
- ± absent radial or ulnar pulses

### Treatment

- assess neurovascular status before reduction: brachial artery, median and ulnar nerves (can become entrapped during manipulation)
- closed reduction under conscious sedation (post-reduction x-rays required)
- Parvin's method: patient lies prone with arm hanging down; apply gentle traction downwards on wrist, as olecranon slips distally, gently lift up the arm at elbow to reduce joint
- long-arm splint with forearm in neutral rotation and elbow in 90° flexion
- early ROM (<2 wk)

### Specific Complications (see *General Fracture Complications*, OR6)

- stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture
- recurrent instability uncommon

## Epicondylitis

- lateral epicondylitis = “tennis elbow”, inflammation of the common extensor tendon as it inserts into the lateral epicondyle
- medial epicondylitis = “golfer’s elbow”, inflammation of the common flexor tendon as it inserts into the medial epicondyle

### Mechanism

- repeated or sustained contraction of the forearm muscles

### Clinical Features

- point tenderness over humeral epicondyle and/or distal to it
- pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
- generally a self-limited condition, but may take 6-18 mo to resolve

### Treatment

- rest, ice, NSAIDs
- use brace/strap
- physiotherapy, stretching and strengthening
- corticosteroid injection
- surgery: percutaneous or open release of common tendon from epicondyle (only after 6-12 mo of conservative therapy)



**Tennis Elbow** = lateral epicondylitis; pain associated with extension of wrist.



### Elbow Joint Injection

Inject at the centre of the triangle formed by the lateral epicondyle, radial head and olecranon.

## Forearm



## Radius and Ulna Fracture

### Mechanism

- commonly a FOOSH or high-energy direct blow
- fractures usually accompanied by displacement due to high force

### Investigations

- x-ray: 1) AP and lateral of forearm; 2) AP, lateral, oblique of elbow and wrist
- CT if fracture is close to joint

### Treatment

- goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
- ORIF with plates and screws; closed reduction with immobilization usually yields poor results for displaced forearm fractures (except in children)

### Complications (see *General Fracture Complications*, OR6)

- soft tissue contracture resulting in limited forearm rotation – surgical release of tissue may be warranted

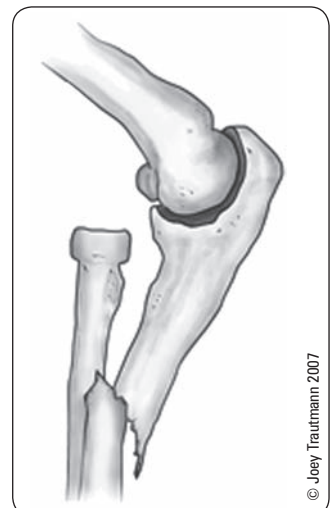


Figure 20. Monteggia fracture



In all isolated ulna fractures, assess proximal radius to rule out a Monteggia fracture.



### Bado Type Classification of Monteggia Fractures

Based on the direction of displacement of the dislocated radial head, generally the same direction as the apex of the ulnar fracture

Type I: anterior dislocation of radial head (60%)

Type II: posterior dislocation of radial head (15%)

Type III: lateral dislocation of radial head (20%)

Type IV – combined: proximal fracture of the ulna and radius, dislocation of the radial head in any direction (<5%)

## Monteggia Fracture

- more common and better prognosis in the pediatric age group when compared to adults

### Definition

- fracture of the proximal ulna with radial head dislocation and proximal radioulnar joint injury (Figure 20)

### Mechanism

- direct blow on the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

### Clinical Features

- decreased rotation of forearm ± palpable lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

### Treatment

- adults: ORIF of ulna with indirect radius reduction in 90% of patients
- splint and early post-op ROM if elbow completely stable, otherwise immobilization in plaster with elbow flexed for 6 wk
- pediatrics: attempt closed reduction and immobilization in plaster with elbow flexed for Bado Type I-III, surgery for Type IV

**Specific Complications** (see *General Fracture Complications*, OR6)

- PIN: most common nerve injury, especially with posterior approach to the radius fixation
- radial head instability/redislocation
- radioulnar synostosis

## Nightstick Fracture

**Definition**

- isolated fracture of ulna without dislocation of radial head

**Mechanism**

- direct blow to forearm (e.g. holding arm up to protect face)

**Treatment**

- non-displaced: below elbow cast (x 10 d) followed by forearm brace (~8 wk)
- displaced: ORIF if >50% shaft displacement or >10° angulation

## Galeazzi Fracture

**Definition**

- fracture of the distal radial shaft with disruption of the DRUJ
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis
- 3x more common than Monteggia fracture

**Mechanism**

- hand FOOSH with axial loading of pronated forearm

**Investigations**

- x-rays
  - shortening of distal radius >5 mm relative to the distal ulna
  - widening of the DRUJ space on AP
  - dislocation of radius with respect to ulna on true lateral

**Treatment**

- ORIF of radius; afterwards assess DRUJ stability by balloting distal ulna relative to distal radius
- if DRUJ is stable and reducible, splint for 10-14 d with early ROM encouraged
- if DRUJ is unstable, ORIF or percutaneous pinning with long arm cast in supination x 6 wk

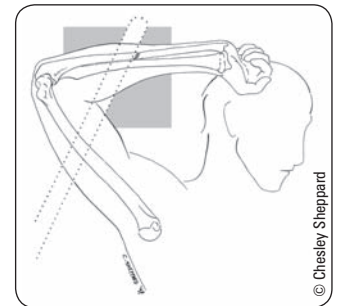


Figure 21. Nightstick fracture

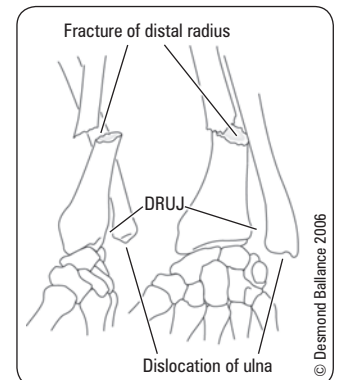


Figure 22. Galeazzi fracture



For all isolated radius fractures assess DRUJ to rule out a Galeazzi fracture.

## Wrist

### Colles' Fracture

**Definition**

- extra-articular transverse distal radius fracture (about 2 cm proximal to the radiocarpal joint) with dorsal displacement ± ulnar styloid fracture

**Epidemiology**

- most common fracture in those >40 yr, especially in women and those with osteoporotic bone

**Mechanism**

- FOOSH

**Clinical Features**

- “dinner fork” deformity (Figures 23 and 24)
- swelling, ecchymoses, tenderness

**Investigations**

- x-ray: AP and lateral wrist

**Treatment**

- goal is to restore radial height, radial inclination (22°), volar tilt (11°) as well as DRUJ stability and useful forearm rotation
- closed reduction (think opposite of the deformity):
  - hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
  - closed reduction: 1) traction with extension (exaggerate injury), 2) traction with ulnar deviation, pronation, flexion (of distal fragment – not at wrist)
  - dorsal slab/below elbow cast for 5-6 wk
  - x-ray x 1 wk for 3 wk and at cessation of immobilization to ensure reduction is maintained
- obtain post-reduction films immediately; repeat reduction if necessary, consider external fixation or ORIF if failure of adequate closed reduction

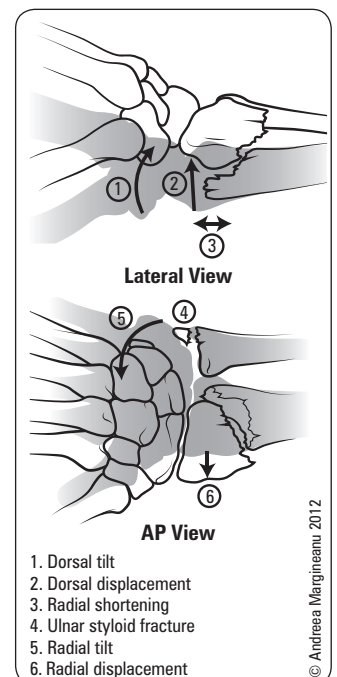


Figure 23. Colles' fracture and associated bony deformity



## Smith's Fracture

### Definition

- volar displacement of the distal radius (i.e. reverse Colles' fracture)

### Mechanism

- fall onto the back of the flexed hand

### Treatment

- usually unstable and needs ORIF
- if patient is poor operative candidate, may attempt non-operative treatment
- closed reduction with hematoma block (reduction opposite of Colles')
- long-arm cast in supination x 6 wk

## Complications of Wrist Fractures

- most common complications are poor grip strength, stiffness, and radial shortening
- distal radius fractures in individuals <40 yr of age are usually highly comminuted and are likely to require ORIF
- 80% have normal function in 6-12 mo

**Table 11. Early and Late Complications of Wrist Fractures**

Early	Late
Difficult reduction $\pm$ loss of reduction	Malunion, radial shortening (Figure 24)
Compartment syndrome	Painful wrist secondary to ulnar prominence
Extensor pollicis longus tendon rupture	Frozen shoulder ("shoulder-hand syndrome")
Acute carpal tunnel syndrome	Post-traumatic arthritis
Finger swelling with venous block	Carpal tunnel syndrome
Complications of a tight cast/splint	CRPS/RSD

## Scaphoid Fracture

### Epidemiology

- common in young men; not common in children or in patients beyond middle age
- most common carpal bone injured
- may be associated with other carpal or wrist injuries (e.g. Colle's fracture)

### Mechanism

- FOOSH: impaction of scaphoid on distal radius, most commonly resulting in a transverse fracture through the middle/'waist' (50%), distal (38%), or proximal (12%) scaphoid

### Clinical Features

- pain with wrist movement
- tenderness in the anatomical "snuff box", over scaphoid tubercle, and pain with long axis compression into scaphoid
- usually undisplaced

### Investigations

- x-ray: PA, lateral, scaphoid views with wrist extension and ulnar deviation x 2 wk
- $\pm$  CT or MRI
- bone scan rarely used
- note:** a fracture may not be radiologically evident up to 2 wk after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 wk later to rule out a fracture. If x-ray still negative order CT or MRI

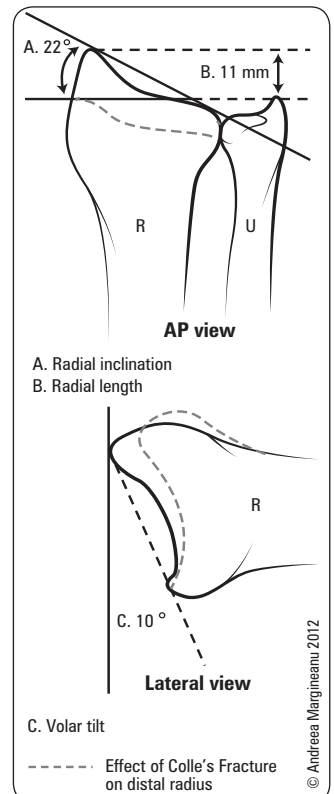
### Treatment

- early treatment critical for improving outcomes
- non-displaced (<1 mm displacement/<15° angulation): long-arm thumb spica cast x 4 wk then short arm cast until radiographic evidence of healing is seen (2-3 mo)
- displaced: ORIF with headless/countersink compression screw is the mainstay treatment, or percutaneous K-wire fixation (uncommon) (Figure 26)



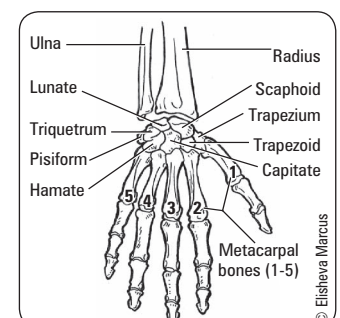
### ORIF Colles' Fracture if Post-reduction Demonstrates:

- Radial shortening >3 mm or,
- Dorsal tilt >10° or,
- Intra-articular displacement/step-off >2 mm



**Figure 24. Normal wrist angles + wrist angles in Colles' fracture**

Note the relative shortening of the radius relative to the ulna on AP view in Colles' fracture



**Figure 25. Carpal bones**



### Scaphoid Fracture Special Tests

Tender snuff box: 100% sensitivity, but 29% specific as positive with many other injuries of radial aspect of wrist with FOOSH.



**Specific Complications** (see *General Fracture Complications*, OR6)

- most common: non-union/mal-union (use bone graft from iliac crest or distal radius with fixation to heal)
- AVN of the proximal fragment
- delayed union (recommend surgical fixation)

**Prognosis**

- fractures of the proximal third of the scaphoid have 70% rate of non-union or AVN
- waist fractures have healing rates of 80-90%
- distal third fractures have healing rates close to 100%



Figure 26. ORIF left scaphoid

## Hand

- see [Plastic Surgery](#), PL22



## Spine

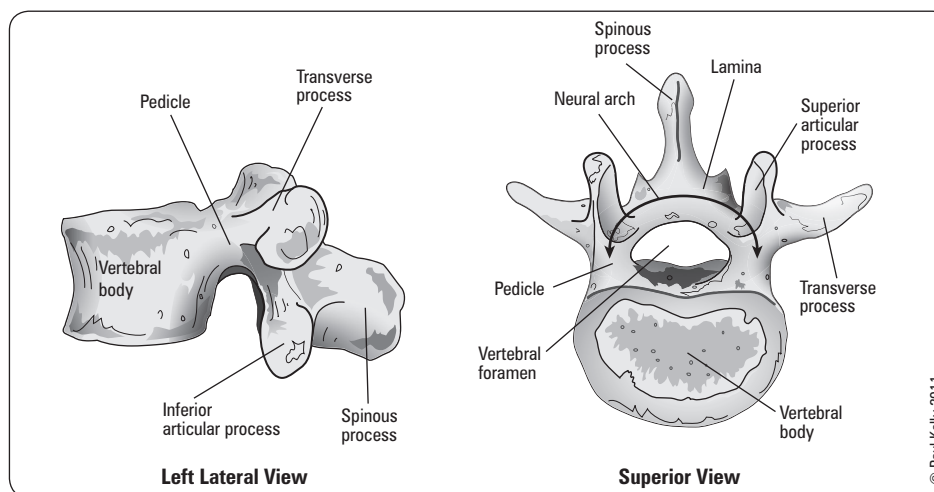


Figure 27. Schematic diagram of vertebral anatomy

Adapted from Moore KL, Agur AMR. *Essential Clinical Anatomy*. 3rd Ed. Philadelphia: Lippincott Williams and Wilkins, 2007, 274

## Fractures of the Spine

- see [Neurosurgery](#), NS33

Table 12. Fracture Type and Column Involvement

Fracture Type	Column Failure	Stable/Unstable	Mechanism
Compression	Anterior	Stable	Compression
Burst	Anterior, middle	± Unstable	High-energy axial loading + flexion
Fracture-dislocation	Anterior, middle, posterior	Unstable	Significant force applied to spine (flexion, extension, distraction, rotation, shear or axial load)
Flexion-distraction	Middle, posterior	± Unstable	MVC (lap belt only) causing flexion and distraction (Chance fracture)

## Cervical Spine

**General Principles**

- C1 (atlas): no vertebral body, no spinous process
- C2 (axis): odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
- nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra), C8 nerve root exits below C7 vertebra
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord



The proximal pole of the scaphoid receives as much as 100% of its arterial blood supply from the radial artery that enters at the distal pole. A fracture through the proximal third disrupts this blood supply and results in a high incidence of AVN/non-union.

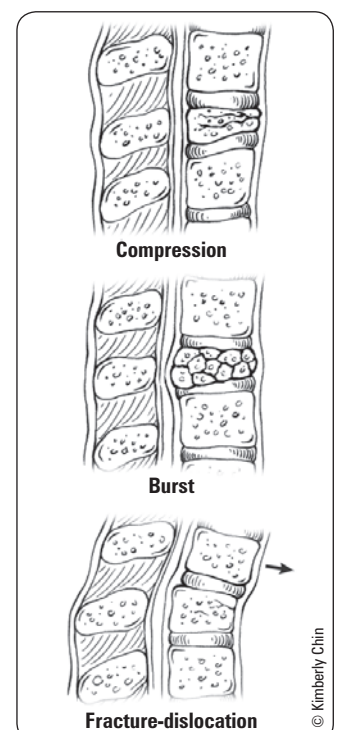


Figure 28. Compression, burst, and dislocation fractures

### Special Testing

- compression test: pressure on head worsens radicular pain
- distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain

**Table 13. Cervical Radiculopathy/Neuropathy**

Root	C5	C6	C7	C8
<b>Motor</b>	Deltoid Biceps Wrist extension	Biceps Brachioradialis	Triceps Wrist flexion Finger extension	Interossei Digital flexors
<b>Sensory</b>	Axillary nerve (patch over lateral deltoid)	Thumb and index finger	Middle finger	Ring and little finger
<b>Reflex</b>	Biceps	Biceps Brachioradialis	Triceps	Finger jerk

### X-Rays for C-Spine

- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- lateral
  - vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
  - angulation: between adjacent vertebral bodies (>11° is abnormal)
  - disc or facet joint widening
  - anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
- oblique: evaluate pedicles and intervertebral foramen
- ± swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
- ± lateral flexion/extension view: evaluate subluxation of cervical vertebrae

### Differential Diagnosis of C-Spine Pain

- neck muscle strain, cervical spondylosis, cervical stenosis, rheumatoid arthritis (spondylitis), traumatic injury, whiplash, myofascial pain syndrome

### C-SPINE INJURY

- see [Neurosurgery](#), NS34



**C-Spine X-Ray in Trauma**  
Must see C7-T1.



#### Canadian C-spine Rule

Used to guide imaging for alert (GCS = 15) and stable patients with suspected C-spine injury  
Obtain radiography if:

- Age ≥65
- Paresthesia in the extremities
- Inability to rotate neck >45° to the left and right
- Dangerous mechanism of injury (e.g. high speed MVC, fall from elevation >5 ft, etc.)

Canadian CT Head and C-Spine (CCC) Study Group.  
Canadian C-Spine Rule Study for alert and stable trauma patients. I. Background and rationale.  
*CEJM* 2002;4:84-90



All trauma patients with suspected C-spine injury require immediate immobilization of C-spine at scene of accident with spine board, C-collar, and sandbags.

## Thoracolumbar Spine

### General Principles

- spinal cord terminates at conus medullaris (L1)
- individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)

### Special Tests

- straight leg raise: passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down posterior/lateral leg to knee ± into foot
- Lasegue maneuver: dorsiflexion of foot during straight leg raise makes symptoms worse or, if leg is less elevated, dorsiflexion will bring on symptoms
- femoral stretch test: with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular symptoms of unilateral pain in lumbar region, buttock, or posterior thigh

**Table 14. Lumbar Radiculopathy/Neuropathy**

Root	L4	L5	S1
<b>Motor</b>	Quadriceps (knee extension + hip adduction) Tibialis anterior (ankle inversion + dorsiflexion)	Extensor hallucis longus Gluteus medius (hip abduction)	Peroneus longus + brevis (ankle eversion) Gastrocnemius + soleus (plantar flexion)
<b>Sensory</b>	Medial malleolus	1st dorsal webspace and lateral leg	Lateral foot
<b>Reflex</b>	Knee (Patellar)	Medial hamstring*	Ankle (Achilles)
<b>Test</b>	Femoral stretch	Straight leg raise	Straight leg raise

\*Unreliable

### Differential Diagnosis of Back Pain

1. mechanical or nerve compression (>90%)
  - degenerative (disc, facet, ligament)
  - peripheral nerve compression (disc herniation)
  - spinal stenosis (congenital, osteophyte, central disc)
  - cauda equina syndrome
2. others (<10%)
  - neoplastic (primary, metastatic, multiple myeloma)
  - infectious (osteomyelitis, TB)
  - metabolic (osteoporosis)
  - traumatic fracture (compression, distraction, translation, rotation)
  - spondyloarthropathies (ankylosing spondylitis)
  - referred (aorta, renal, ureter, pancreas)

### DEGENERATIVE DISC DISEASE

- loss of vertebral disc height with age results in:
  - bulging and tears of annulus fibrosus
  - change in alignment of facet joints
  - osteophyte formation
- can cause back-dominant pain
- management
  - non-operative
    - ♦ staying active with modified activity
    - ♦ back strengthening
    - ♦ NSAIDs
    - ♦ do not treat with opioids; no proven efficacy of spinal traction or manipulation
  - operative – rarely indicated
    - ♦ decompression ± fusion
    - ♦ no difference in outcome between non-operative and surgical management at 2 yr

Table 15. Types of Low Back Pain

	Mechanical Back Pain		Direct Nerve Root Compression	
	Disc Origin	Facet Origin	Spinal Stenosis	Root Compression
<b>Pain Dominance</b>	Back	Back	Leg	Leg
<b>Aggravation</b>	Flexion	Extension, standing, walking	Exercise, extension, walking, standing	Flexion
<b>Onset</b>	Gradual	More sudden	Congenital or acquired	Acute leg ± back pain
<b>Duration</b>	Long (weeks, months)	Shorter (days, weeks)	Acute or chronic history (weeks to months)	Short episodes Attacks (minutes)
<b>Treatment</b>	Relief of strain, exercise	Relief of strain, exercise	Relief of strain, exercise	Relief of strain, exercise + surgical decompression if progressive or severe deficit

### SPINAL STENOSIS

- definition: narrowing of spinal canal <10 mm
- etiology: congenital (idiopathic, osteopetrosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylosis, Paget's disease, trauma)
- clinical features
  - ± bilateral back and leg pain
  - neurogenic claudication (see Table 16)
  - ± motor weakness
  - normal back flexion; difficulty with back extension
- investigations: CT/MRI reveals narrowing of spinal canal, but gold standard = CT myelogram
- treatment
  - non-operative: vigorous physiotherapy (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
  - operative: decompression surgery if conservative methods failed >6 mo

Table 16. Differentiating Claudication

	Neurogenic	Vascular
<b>Aggravation</b>	With standing or exercise Walking distance variable	Walking set distance
<b>Alleviation</b>	Change in position (usually flexion, sitting, lying down)	Stop walking
<b>Time</b>	Relief in ~10 min	Relief in ~2 min
<b>Character</b>	Neurogenic ± neurological deficit	Muscular cramping



Cauda equina syndrome and ruptured aortic aneurysms are causes of low back pain that are considered surgical emergencies.



#### Red Flags for

##### BACK PAIN

Bowel or bladder dysfunction  
Anesthesia (saddle)  
Constitutional symptoms/malignancy  
Chronic disease  
Paresthesias  
Age > 50  
IV drug use  
Neuromotor deficits

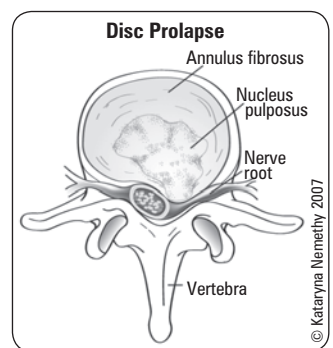


Figure 29. Disc herniation causing nerve root compression



Neurogenic claudication is position dependant. Vascular claudication is exercise dependant.

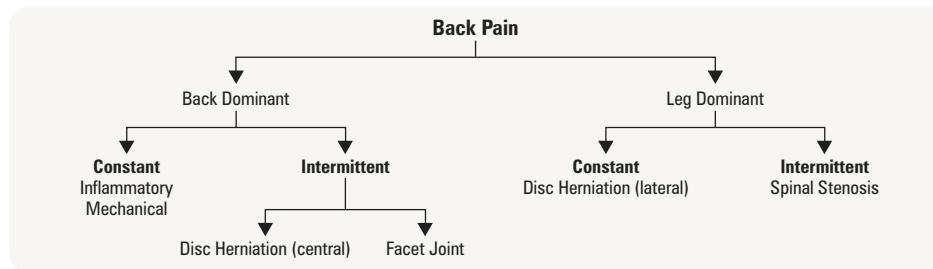


Figure 30. Approach to back pain

### MECHANICAL BACK PAIN

- definition: back pain NOT due to prolapsed disc or any other clearly defined pathology
- clinical features
  - dull backache aggravated by activity
  - morning stiffness
  - no neurological signs
- treatment: symptomatic (analgesics, physiotherapy)
- prognosis: symptoms may resolve in 4-6 wk, others become chronic

### LUMBAR DISC HERNIATION

- definition: tear in annulus fibrosus allows protrusion of nucleus pulposus causing either a central, posterolateral, or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
- etiology: usually a history of flexion-type injury
- clinical features
  - back dominant pain (central herniation) or leg dominant pain (lateral herniation)
  - tenderness between spines at affected level
  - muscle spasm ± loss of normal lumbar lordosis
  - neurological disturbance is segmental and varies with level of central herniation
    - ♦ motor weakness (L4, L5, S1)
    - ♦ diminished reflexes (L4, S1)
    - ♦ diminished sensation (L4, L5, S1)
  - +ve straight leg raise
  - +ve Lasague test
  - bowel or bladder symptoms, decreased rectal tone suggests cauda equina syndrome due to central disc herniation – surgical emergency
- investigations: MRI, consider a post void residual volume to check for urinary retention
- treatment
  - symptomatic
    - ♦ extension protocol (physiotherapy)
    - ♦ NSAIDs
  - 90% resolve in 3 mo. Surgical discectomy reserved for progressive neurological deficit, failure of symptoms to resolve within 3 mo, or cauda equina syndrome due to central disc herniation

### SPONDYLOLYSIS

- definition: defect in the pars interarticularis with no movement of the vertebral bodies
- etiology
  - trauma: gymnasts, weightlifters, backpackers, loggers, labourers
- clinical features: activity-related back pain, pain with unilateral extension (Michelis' test)
- investigations
  - oblique x-ray: "collar" break in the "Scottie dog's" neck
  - bone scan
  - CT scan
- treatment: activity restriction, brace, stretching exercise

### SPONDYLOLISTHESIS

- definition: defect in pars interarticularis causing a forward slip of one vertebra on another usually at L5-S1, less commonly at L4-5
- etiology: congenital (children), degenerative (adults), traumatic, pathological, teratogenic
- clinical features: lower back pain radiating to buttocks



MRI abnormalities (e.g. spinal stenosis, disc herniation) are quite common in both asymptomatic and symptomatic individuals and are not necessarily an indication for intervention without clinical correlation.



#### Sciatica

- Most common symptom of radiculopathy (L4-S3)
- Leg dominant, constant, burning pain
- Pain radiates down leg ± foot
- Most common cause = disc herniation

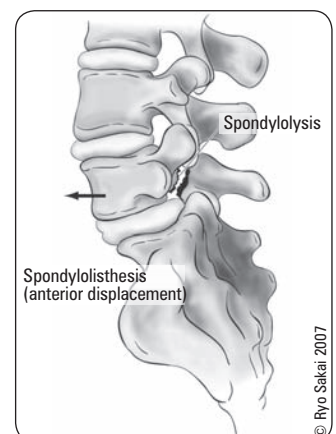


Figure 31. Spondylolysis, spondylolisthesis

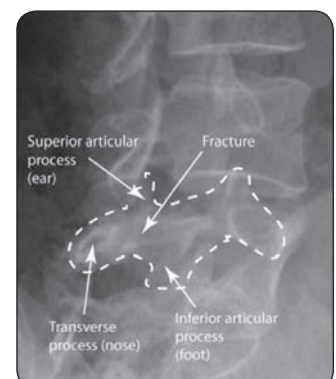


Figure 32. "Scottie dog" fracture

**Table 17. Classification and Treatment of Spondylolisthesis**

Class	Percentage of Slip	Treatment
1	0-25%	Symptomatic operative fusion only for intractable pain
2	25-50	Same as above
3	50-75	Decompression for spondylolisthesis and spinal fusion
4	75-100	Same as above
5	>100	Same as above

**Specific Complications**

- may present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

## Pelvis

### Pelvic Fracture

**Mechanism**

- young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- elderly: fall from standing height, low energy trauma
- lateral compression (most common), vertical shear, or anteroposterior compression fractures

**Clinical Features**

- local swelling, tenderness
- deformity of lower extremity
- pelvic instability

**Investigations**

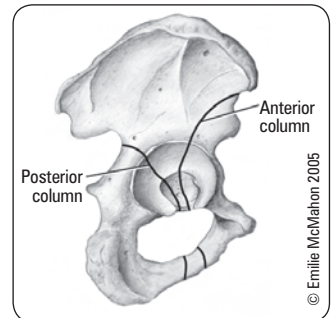
- x-ray: AP pelvis, inlet and outlet views, Judet views (obturator and iliac oblique for acetabular fracture)
  - 6 cardinal radiographic lines of the acetabulum: ilioischial line, iliopectineal line, tear drop, roof, posterior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture

**Classification****Table 18. Tile Classification of Pelvic Fractures** (see Figure 34)

Type	Stability	Description
<b>A</b>	Rotationally stable Vertically stable	A1: fracture not involving pelvic ring A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture)
<b>B</b>	Rotationally unstable Vertically stable	B1: open book B2: lateral compression – ipsilateral B3: lateral compression – contralateral
<b>C</b>	Rotationally unstable Vertically unstable	C1: unilateral C2: bilateral C3: associated acetabular fracture

**Treatment**

- ABCDEs
- assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)
  - if involved, the fracture is considered an open fracture
- stable fractures: non-operative treatment, protected weight bearing
- emergency management
  - IV fluids/blood
  - pelvic binder/sheeting
  - external fixation vs. emergent angiography/embolization
  - $\pm$  laparotomy (if FAST/DPL positive)
- indications for operative treatment
  - unstable pelvic ring injury
  - disruption of anterior and posterior SI ligament
  - symphysis diastasis >2.5 cm
  - vertical instability of the posterior pelvis

**Figure 33. Pelvic columns****Possible Radiological Findings:**

- Pubic rami fractures: superior/inferior
- Pubic symphysis diastasis: common in AP compression (N=5 mm)
- Sacral fractures: common in lateral compression
- SI joint diastasis: common in AP compression (N=1-4 mm)
- Disrupted anterior column (iliopectineal line) or posterior column (ilioischial line)
- "Teardrop" displacement: acetabular fracture
- Iliac, ischial avulsion fractures
- Displacement of the major fragment: superior (VS), open book (APC), bucket handle (LC)

**Type A  
Stable Avulsion Fracture****Type B  
Open Book****Type C  
Unstable Vertical Fracture****Figure 34. Illustration of the Tile classification of pelvic fractures**

**Specific Complications** (see *General Fracture Complications*, OR6)

- **hemorrhage (life-threatening)**
- injury to rectum or urogenital structures
- obstetrical difficulties, sexual and voiding dysfunction
- persistent SI joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high risk of DVT/PE

## Hip

### Hip Dislocation

- full trauma survey (see [Emergency Medicine, Initial Patient Assessment/Management](#), ER2)
- examine for neurovascular injury PRIOR to open or closed reduction
- reduce hip dislocations ASAP (ideally within 6 h) to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 wk post-reduction
- also see *Hip Dislocation after THA*, OR28

**ANTERIOR HIP DISLOCATION**

- mechanism: posteriorly directed blow to knee with hip widely abducted
- clinical features: shortened, abducted, externally rotated limb
- treatment
  - closed reduction under conscious sedation/GA
  - post-reduction CT to assess joint congruity

**POSTERIOR HIP DISLOCATION**

- most frequent type of hip dislocation
- mechanism: severe force to knee with hip flexed and adducted
  - e.g. knee into dashboard in motor vehicle collision (MVC)
- clinical features: shortened, adducted and internally rotated limb
- treatment
  - closed reduction under conscious sedation/GA only if associated femoral neck fracture
  - ORIF if unstable, intra-articular fragments or posterior wall fracture
  - post-reduction CT to assess joint congruity and fractures
  - if reduction is unstable, put in traction x 4-6 wk

**CENTRAL HIP DISLOCATION (rare)**

- traumatic injury where femoral head is pushed medially through acetabulum

**COMPLICATIONS FOR ALL HIP DISLOCATIONS**

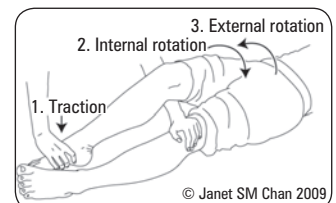
- post-traumatic osteoarthritis
- AVN of femoral head
- fracture of femoral head, neck, or shaft
- sciatic nerve palsy in 25% (10% permanent)
- HO
- thromboembolism – DVT/PE



Up to 50% of patients with hip dislocations suffer fractures elsewhere at the time of injury.

**Rochester Method to Reduce Dislocations**

- Patient lying supine with hip and knee flexed on injured side
- Surgeon stands on patient's injured side
- Surgeon passes one arm under patient's flexed knee, reaching to place that hand on patient's other knee (thus supporting patient's injured leg)
- With other hand, surgeon grasps patient's ankle on injured side, applying traction, while assistant stabilizes pelvis
- Reduction via traction, int. rotation, then ext. rotation once femoral head clears acetabular rim



© Janet SM Chan 2009

**Figure 35. Rochester method**

**X-Ray Features of Subcapital Hip Fractures**

- Disruption of Shenton's line (a radiographic line drawn along the upper margin of the obturator foramen, extending along the inferomedial side of the femoral neck)
- Altered neck-shaft angle (normal is 120-130°)

## Hip Fracture

**General Features**

- acute onset of hip pain
- unable to weight-bear
- shortened and externally rotated leg
- painful ROM



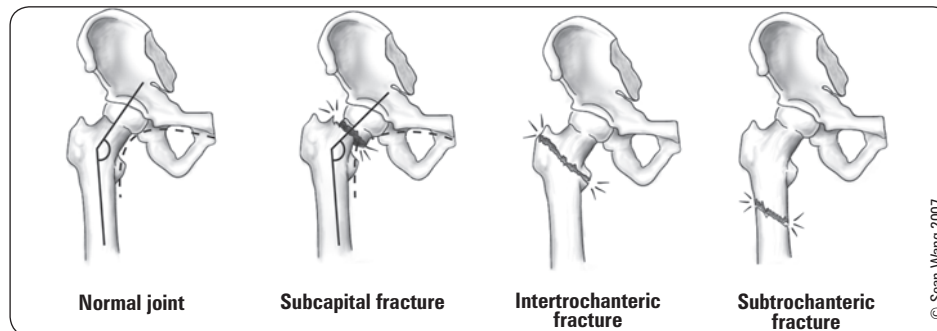


Figure 36. Subcapital, intertrochanteric, subtrochanteric fractures

Table 19. Overview of Hip Fractures

Fracture Type	Definition	Mechanism	Special Clinical Features	Investigations	Treatment	Complications
<b>Femoral Neck (Subcapital)</b>	Intracapsular (See <i>Garden Classification</i> , Table 20)	Young: MVC, fall from height Elderly: fall from standing, rotational force	Same as general	X-ray: AP hip, AP pelvis, cross table lateral hip	See Table 20	DVT, non-union, AVN
<b>Intertrochanteric</b> Stable: intact posteromedial cortex Unstable: non-intact posteromedial cortex	Extracapsular fracture including the greater and lesser trochanters and transitional bone between the neck and shaft	Same as femoral neck fracture Direct or indirect force transmitted to the intertrochanteric area	Ecchymosis at back of upper thigh	X-ray: AP pelvis, AP/lateral hip	Closed reduction under fluoroscopy then dynamic hip screw or IM nail	DVT, varus displacement of prox. fragment, malrotation, non-union, failure of fixation device
<b>Subtrochanteric</b>	Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft	Young: high energy trauma Elderly: osteopenic bone + fall, pathological fracture	Ecchymosis at back of upper thigh	X-ray: AP pelvis, AP/lateral hip and femur	Closed/open under fluoroscopy then plate fixation or IM nail	Malalignment, non-union, wound infection

Table 20. Garden Classification of Femoral Neck Fractures

Type	Displacement	Extent	Alignment	Trabeculae	Treatment
I	None	"Incomplete"	Valgus or neutral	Malaligned	Internal fixation to prevent displacement (valgus impacted fracture)
II	None	Complete	Neutral	Aligned	Internal fixation to prevent displacement
III	Some	Complete	Varus	Malaligned	Young: ORIF Elderly: hemi-/total hip arthroplasty
IV	Complete	Complete	Varus	Aligned	Young: ORIF Elderly: hemi-/total hip arthroplasty

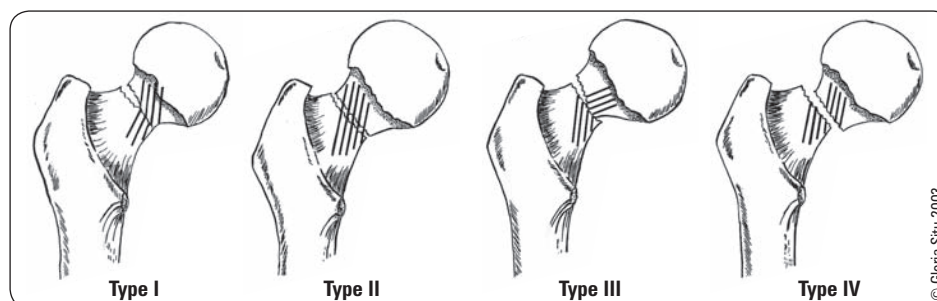


Figure 37. Garden classification of femoral neck fractures



**DVT Prophylaxis in Hip Fractures**  
LMWH (i.e. enoxaparin 40 mg SC bid), fondaparinux, low dose heparin on admission, do not give < 12 h before surgery.



**AVN of Femoral Head**

- Distal to proximal blood supply along femoral neck to head (medial and lateral femoral circumflex arteries)
- Susceptible to AVN if blood supply disrupted
- Etiology: femoral neck fracture, chronic systemic steroid use, slipped capital femoral epiphysis, Legg-Calve-Perthes, SLE, RA

## Arthritis of the Hip

### Etiology

- OA, inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders or septic arthritis

### Clinical Features

- pain (groin, medial thigh) and stiffness aggravated by activity
- morning stiffness > 1 h, multiple joint swelling, hand nodules (RA)
- decreased ROM (internal rotation is lost first)
- crepitus
- ± fixed flexion contracture leading to apparent limb shortening (Thomas test)
- ± Trendelenberg sign

**Investigations**

- x-ray
  - OA: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes
  - RA: osteopenia, erosion, joint space narrowing, subchondral cysts, symmetric joint space narrowing
- bloodwork: ANA, RF

**Treatment**

- non-operative: weight reduction, activity modification, physiotherapy, analgesics, walking aids
- operative: realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
- complications with arthroplasty: component loosening, dislocation, HO, thromboembolism, infection, neurovascular injury, limb length discrepancy
- arthroplasty is standard of care in most patients with hip arthritis



**DVT Prophylaxis in Elective THA**  
(continue 10-35 d post-op)  
Fondaparinux, low molecular weight heparin, or coumadin.

## Hip Dislocation after Total Hip Arthroplasty

**Etiology**

- THA that is unstable when hip is flexed, adducted and internally rotated or extended and externally rotated (avoid flexing hip  $>90^\circ$  or crossing legs for approximately 6 wk after surgery)

**Epidemiology**

- occurs in 1-4% of primary THA and 10-16% of revision THAs
- risk factors: neurological impairment, post-traumatic arthritis, revision surgery, substance abuse

**Treatment**

- external abduction splint to prevent hip adduction
- constrained acetabular component for recurrent dislocation if no issue with position of acetabular/femoral implants + knee immobilizer

**Complications**

- sciatic nerve palsy in 25% (10% permanent)
- HO

## Femur



## Femoral Diaphysis Fracture

**Mechanism**

- high energy trauma (MVC, fall from height, gunshot wound)
- in children, can result from low energy trauma (spiral fracture)

**Clinical Features**

- shortened, externally rotated leg (if fracture displaced)
- inability to weight-bear
- often open injury, always a Gustilo III (see Table 4)

**Investigations**

- AP pelvis, AP/lateral hip, femur, knee

**Complications**

- hemorrhage requiring transfusion
- fat embolism leading to ARDS
- extensive soft tissue damage
- ipsilateral hip dislocation/fracture
- nerve injury

**Treatment**

- stabilize patient
- immobilize leg
- ORIF with antegrade or retrograde IM nail, external fixator for unstable patients, open fractures, or highly vascular areas, or plate and screws for open growth plates within 24 h
- early mobilization and strengthening

## Distal Femoral Fracture

### Mechanism

- direct high energy force or axial loading
- three types (Figure 38) in addition to classification as intra-articular or extra-articular

### Clinical Features

- extreme pain
- knee effusion (hemarthrosis)
- shortened, externally rotated leg if displaced

### Treatment

- ORIF if displaced or intra-articular; may choose to manage nonoperatively if nondisplaced or incomplete fracture
- early mobilization and strengthening

### Complications (see *General Fracture Complications*, OR6)

- femoral artery tear
- nerve injury
- extensive soft tissue injury
- angulation deformities

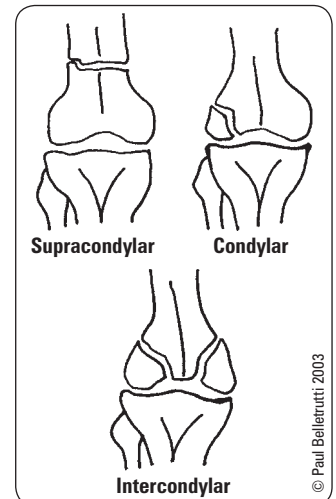


Figure 38. Distal femoral fractures

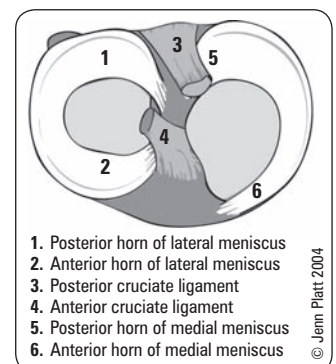


Figure 39. Diagram of the right tibial plateau

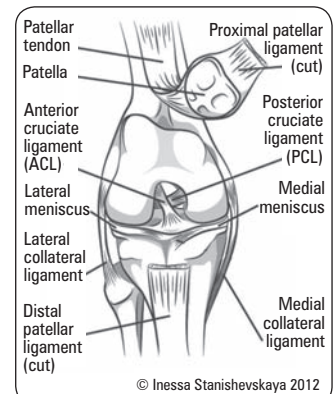


Figure 40. Knee ligament and anatomy



### 6 Degrees of Freedom of the Knee

- Flex. and ext.
- Ext. and int. rotation
- Varus and valgus angulation
- Ant. and post. glide
- Med. and lat. shift
- Compression and distraction



On physical exam of the knee, do not forget to evaluate the hip!

## Knee

### Evaluation of Knee

#### Common Complaints

- general orthopedic history
- also inquire about common knee symptoms
  - locking: mechanical block to extension
    - ♦ torn meniscus/loose body in joint
  - pseudo-locking: limited ROM without mechanical block
    - ♦ effusion, muscle spasm after injury, arthritis
  - painful clicking (audible)
    - ♦ torn meniscus
  - giving way: instability
    - ♦ cruciate ligament or meniscal tear, patellar dislocation

#### Special Tests of the Knee

- **anterior and posterior drawer tests** (see Figure 41)
  - demonstrate ACL and PCL, respectively
    - ♦ knee flexed at 90°, foot immobilized, hamstrings released
    - ♦ if able to sublux tibia anteriorly (anterior drawer test), then ACL may be torn
    - ♦ if able to sublux tibia posteriorly (posterior drawer test), then PCL may be torn
    - ♦ anterior drawer test for ACL: 3.8 positive likelihood ratio, 0.30 negative likelihood ratio
- **Lachmann test**
  - demonstrates torn ACL
  - hold knee in 10–20° flexion, stabilizing the femur
  - try to sublux tibia anteriorly on femur
  - similar to anterior drawer test, more reliable due to less muscular stabilization
  - for ACL: 25.0 positive likelihood ratio, 0.1 negative likelihood ratio
- **Thessaly test**
  - demonstrates meniscal tear
  - patient stands flat footed on one leg while the examiner provides his or her hands for balance. The patient then flexes the knee to 20° and rotates the femur on the tibia medially and laterally three times while maintaining the 20° flexion
  - positive for a meniscal tear if the patient experiences medial or lateral joint line discomfort.
  - for medial meniscus: 29.67 positive likelihood ratio, 0.11 negative likelihood ratio
  - for lateral meniscus: 23.0 positive likelihood ratio, 0.083 negative likelihood ratio
- **posterior sag sign**
  - demonstrates torn PCL
  - may give a false positive anterior draw sign
  - flex knees and hips to 90°, hold ankles and knees
  - view from the lateral aspect
  - if one tibia sags posteriorly compared to the other, its PCL is torn

- **pivot shift sign**
  - demonstrates torn ACL
  - start with the knee in extension
  - internally rotate foot, slowly flex knee while palpating and applying a valgus force
  - normal knee will flex smoothly
  - if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the "pivot")
  - reverse pivot shift (start in flexion, externally rotate, apply valgus and extend knee) suggests torn PCL
  - composite assessment for ACL: 25.0 positive likelihood ratio, 0.04 negative likelihood ratio
  - composite assessment for PCL: 21.0 positive likelihood ratio, 0.05 negative likelihood ratio
- **collateral ligament stress test**
  - palpate ligament for "opening" of joint space while testing
  - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
  - repeat tests with knee in 20° flexion to relax joint capsule
  - opening only in 20° flexion due to MCL damage only
  - opening in 20° of flexion and full extension is due to MCL, cruciate, and joint capsule damage
- **tests for meniscal tear**
  - joint line tenderness
    - ♦ joint line pain when palpated
    - ♦ palpate one side at a time and watch patient's eyes
    - ♦ for meniscal tear: 0.9 positive likelihood ratio, 1.1 negative likelihood ratio
  - crouch compression test
    - ♦ joint line pain when squatting (anterior pain suggests patellofemoral pathology)
  - McMurray's test useful collaborative information (see Figure 42)
    - ♦ with knee in flexion, palpate joint line for painful "pop/click"
    - ♦ internally rotate foot, varus stress, and extend knee to test lateral meniscus
    - ♦ externally rotate foot, valgus stress, and extend knee to test medial meniscus
    - ♦ for meniscal tear: 1.3 positive likelihood ratio, 0.8 negative likelihood ratio
  - composite assessment for meniscal tears: 2.7 positive likelihood ratio, 0.4 negative likelihood ratio

## X-Rays

- AP standing, lateral
- skyline: tangential view with knees flexed at 45° to see patellofemoral joint
- 3-foot standing view: useful in evaluating leg length and varus/valgus alignment
- Ottawa Knee Rules (see [Emergency Medicine](#), ER17)

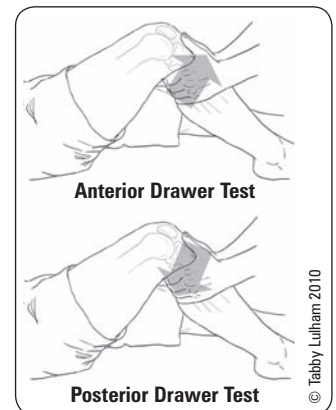


Figure 41. Anterior and posterior drawer test

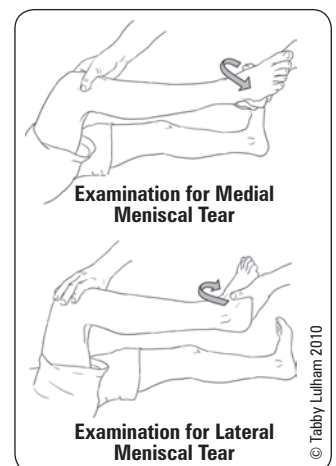


Figure 42. McMurray test

## Cruciate Ligament Tears

- ACL tear much more common than PCL tear

Table 21. Comparison of ACL and PCL Injuries

	Anterior Cruciate Ligament	Posterior Cruciate Ligament
<b>Anatomy</b>	From medial wall of lateral femoral condyle to the anteromedial and posterolateral intercondyloid eminence of the tibial plateau	Lateral wall of medial femoral condyle to posterior intercondyloid eminence of the tibial plateau
<b>Mechanism</b>	Sudden deceleration Hyperextension and internal rotation of tibia on femur (i.e. "plant and turn")	Sudden posterior displacement of tibia when knee is flexed or hyperextended (e.g. dashboard MVC injury)
<b>History</b>	Audible "pop" Immediate swelling Knee "giving way" Inability to continue activity	Audible "pop" Immediate swelling Pain with push off Cannot descend stairs
<b>Physical</b>	Effusion (hemarthrosis) Posterolateral joint line tenderness Positive anterior drawer Positive Lachmann Pivot shift Test for MCL, meniscal injuries	Effusion (hemarthrosis) Anteromedial joint line tenderness Positive posterior drawer Reverse pivot shift Other ligamentous, bony injuries
<b>Treatment</b>	Stable knee with minimal functional impairment: immobilization 2-4 wk with early ROM and strengthening High demand lifestyle: ligament reconstruction	Unstable knee or young person/high-demand lifestyle: ligament reconstruction Posterior sag



### Knee History

**CLIPS**  
Clicking  
Locking  
Instability  
Pain (location)  
Swelling



Physical examination difficult in acute knee injuries. Immobilize leg and re-examine in one week.

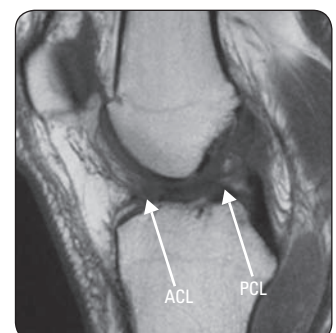


Figure 43. T1 MRI of torn ACL and PCL

## Collateral Ligament Tears

### Mechanism

- valgus force to knee = MCL tear
- varus force to knee = LCL tear

### Clinical Features

- swelling/effusion
- tenderness above and below joint line medially (MCL) or laterally (LCL)
- joint laxity with varus or valgus force to knee
  - laxity with endpoint suggests partial tear
  - laxity with no endpoint suggests a complete tear
- test for other injuries (e.g. O'Donoghue's unhappy triad), common peroneal nerve injury

### Treatment

- partial tear: immobilization x 2-4 wk with early ROM and strengthening
- complete tear: immobilization at 30° flexion
- multiple ligamentous injuries: surgical repair of ligaments



Partial ligamentous tears are much more painful than complete ligamentous tears.



### O'Donoghue's Unhappy Triad

- ACL rupture
- MCL rupture
- Meniscal damage (medial and/or lateral)



### Tissue Sources for ACL Reconstruction

- Hamstring
- Middle 1/3 patellar tendon (bone-patellar-bone)
- Allograft (e.g. cadaver)



ACL tear more common than PCL tear  
MCL tear more common than LCL tear

## Meniscal Tears

- medial tear much more common than lateral tear

### Mechanism

- twisting force on knee when it is partially flexed (e.g. stepping down and turning)
- requires moderate trauma in young person but only mild trauma in elderly due to degeneration

### Clinical Features

- immediate pain, difficulty weight-bearing, instability and clicking
- increased pain with squatting and/or twisting
- effusion (hemarthrosis) with insidious onset (24-48 h after injury)
- joint line tenderness medially or laterally
- locking of knee (if portion of meniscus mechanically obstructing extension)

### Investigations

- MRI, arthroscopy

### Treatment

- if not locked: ROM and strengthening (NSAIDs)
- if locked or failed above: arthroscopic repair/partial meniscectomy

## Quadriceps/Patellar Tendon Rupture

### Mechanism

- sudden forceful contraction of quadriceps during an attempt to stop
- more common in obese patients and those with pre-existing degenerative changes in tendon
  - DM, SLE, RA, steroid use, renal failure on dialysis

### Clinical Features

- inability to extend knee or weight-bear
- possible audible "pop"
- patella in lower or higher position with palpable gap above or below patella respectively
- may have an effusion

### Investigations

- ask patient to straight leg raise
- knee x-ray to rule out patellar fracture
- lateral view: patella alta with patella tendon rupture, patella baja (infera) with quadriceps tendon rupture

### Treatment

- nonoperative treatment for incomplete tears with preserved extension of knee
- surgical repair of tendon indicated for complete ruptures
- early surgical repair: better outcomes compared with delayed repair (>6 wk post injury)
- delayed repair complicated by quadriceps contracture, patella migration, and adhesions



Patella alta = high riding patella  
Patella baja (infera) = low riding patella

## Dislocated Knee



### Mechanism

- high energy trauma
- by definition, caused by tears of multiple ligaments

### Clinical Features

- classified by relation of tibia with respect to femur
  - anterior, posterior, lateral, medial, rotary
- knee instability
- effusion
- pain
- ischemic limb

### Investigations

- x-rays: AP, lateral, skyline
  - associated radiographic findings include tibial plateau fracture dislocations, proximal fibular fractures, and avulsion of fibular head
- ankle brachial index (abnormal if  $<0.9$ )
- arteriogram if abnormal vascular exam (such as abnormal pedal pulses)

### Treatment

- urgent closed reduction
  - complicated by interposed soft tissue
- assessment of peroneal nerve, tibial artery, and ligamentous injuries
- repair of associated injuries; also may need decompressive fasciotomy especially if vascular repair undertaken
- knee immobilization x 6-8 wk

### Specific Complications

- high incidence of associated injuries
  - popliteal artery tear
  - peroneal nerve injury
  - capsular tear
- chronic: instability, stiffness, post-traumatic arthritis

## Patella

### Patellar Fracture

#### Mechanism

- direct blow to the patella: fall, MVC (dashboard)
- indirect trauma by sudden flexion of knee against contracted quadriceps

#### Clinical Features

- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- $\pm$  effusion/hemarthrosis

#### Investigations

- x-rays: AP, lateral, skyline
- consider bipartite patella: congenitally unfused ossification centres with smooth margins on x-ray

#### Treatment

- goal: restore extensor mechanism with maximal articular congruency
- non-displaced (step-off  $<2-3$  mm and fracture gap  $<1-4$  mm)
  - straight leg immobilization 1-4 wk with hinged knee brace
  - physiotherapy: quadriceps strengthening when pain has subsided
- displaced: ORIF ( $>2$  mm)
- comminuted: ORIF; may require partial/complete patellectomy
- disrupted extensor mechanism: ORIF

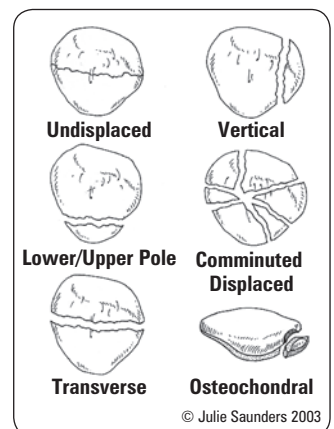


Figure 44. Types of patellar fractures



#### Complications

- Symptomatic wiring
- Hardware failure
- Knee stiffness
- Nonunion
- Infection



## Patellar Dislocation

### Mechanism

- lateral displacement of patella after contraction of quadriceps against a flexed knee

### Risk Factors

- young, female
- obesity
- high-riding patella (patella alta)
- knock-knees (genu valgus)
- Q-angle (quadriceps angle)  $\geq 20^\circ$  (see Figure 45)
- shallow intercondylar groove
- weak vastus medialis
- tight lateral retinaculum

### Clinical Features

- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced
- +ve patellar apprehension test
  - patient apprehensive when examiner laterally displaces patella
- often recurrent, self-reducing
- concomitant MCL injury

### Investigations

- x-rays: AP, lateral, skyline view of patella
  - check for fracture of medial patella and lateral femoral condyle

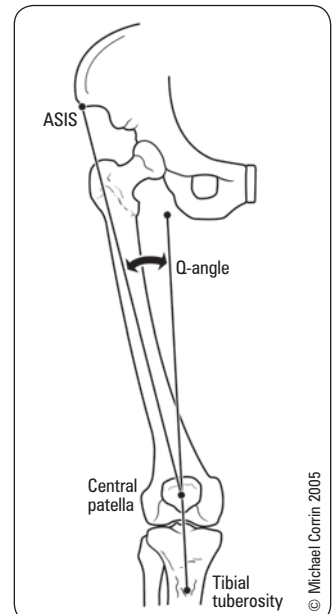
### Treatment

- non-operative first
  - knee immobilization x 4-6 wk
  - progressive weight bearing and isometric quadriceps strengthening
- if recurrent
  - surgical tightening of medial capsule and release of lateral retinaculum, possible tibial tuberosity transfer, or proximal tibial osteotomy



### Patellar Open Reduction and Internal Fixation

- Longitudinal midline excision over patella
- Tension-band wiring fixation
- Preserve patellar bone
- Antibiotic, debridement, early fixation in open fracture



**Figure 45. Q-angle**

The angle between a vertical line through the patella and tibial tuberosity and a line from the ASIS to the patella. The larger the angle the greater the amount of lateral force on the knee (normal  $< 20^\circ$ ).

## Patellofemoral Syndrome (Chondromalacia Patellae)

### Mechanism

- softening, erosion and fragmentation of articular cartilage, predominantly medial aspect of patella
- commonly seen in active young females

### Predisposing Factors

- malalignment causing patellar maltracking (Q angle  $\geq 20^\circ$ , genu valgus)
- post-trauma
- deformity of patella or femoral groove
- recurrent patellar dislocation, ligamentous laxity
- excessive knee strain (athletes)

### Clinical Features

- deep, aching anterior knee pain
  - exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting
- sensation of instability, pseudolocking
- pain with extension against resistance through terminal  $30-40^\circ$
- swelling rare, minimal if present

### Investigations

- x-rays: AP, lateral, skyline

### Treatment

- non-operative
  - continue non-impact activities
  - NSAIDs
  - physiotherapy: quadriceps strengthening
- surgical with refractory patients
  - tibial tubercle elevation
  - arthroscopic shaving/debridement
  - lateral release of retinaculum



Pain with firm compression of patella into medial femoral groove is pathognomonic of patellofemoral syndrome.

# Tibia

## Tibial Plateau Fracture

### Mechanism

- axial loading (e.g. fall from height)
- femoral condyles driven into proximal tibia
- can result from minor trauma in osteoporotics

### Clinical Features

- lateral fractures more common than medial
- medial fractures require higher energy – often have concomitant vascular injuries
- knee effusion
- inability to bear weight
- swelling

### Classification

- Schatzker classification (see sidebar)

### Investigations

- x-rays: AP, lateral
- CT: pre-operative planning

### Treatment

Approach #1 (based on amount of depression seen on x-ray)	If depression on x-ray is <3 mm: Straight leg immobilization x 4-6 wk with progressive ROM weight bearing If depression is >3 mm: ORIF often requiring bone grafting to elevate depressed fragment
Approach #2 (based on varus/valgus instability)	If minimal varus/valgus instability (<15°): Straight leg immobilization x 4-6 wk with progressive ROM weight bearing If significant varus/valgus instability (>15°): ORIF often requiring bone grafting to elevate depressed fragment

### Specific Complications (see General Fracture Complications, OR6)

- ligamentous injuries
- meniscal lesions
- AVN
- infection
- osteoarthritis



#### Schatzker Classification

Type	Description
I	Involvement of lateral plateau split fracture
II	Involvement of lateral plateau: split depression fracture
III	Involvement of lateral plateau: pure depression fracture
IV	Medial plateau fracture
V	Bicondylar plateau fracture
VI	Bicondylar with metaphyseal/diaphyseal involvement

## Tibial Shaft Fracture

### Mechanism

- numerous, including MVC, falls, sporting injuries

### Clinical Features

- open vs. closed
- amount of displacement
- neurovascular status
- most commonly fractured long bone
- most common open fracture

### Investigations

- x-rays: AP, lateral, skyline

### Treatment

- closed
  - minimally displaced: straight leg cast x 4-6 wk with early weight bearing
  - displaced: ORIF with reamed IM nail, plate and screws, or external fixator
- open
  - external fixation or IM nail
  - vascularized coverage of soft tissue defects (often heal poorly)

### Specific Complications (see General Fracture Complications, OR6)

- high incidence of neurovascular injury and compartment syndrome
- poor soft tissue coverage



Tibial shaft fractures have high incidence of compartment syndrome and are often associated with soft tissue injuries.



**Figure 46. Tibial shaft fracture treated with intramedullary nail and screws**

# Ankle

## Evaluation of Ankle and Foot Complaints

### Special Tests

- anterior drawer: examiner attempts to displace the foot anteriorly against a fixed tibia
- talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated by x-ray

### X-Ray

- AP, lateral
- mortise view: ankle at 15° of internal rotation
  - gives true view of ankle joint
  - joint space should be symmetric with no talar tilt
- Ottawa Ankle Rules should guide use of x-ray (see sidebar); nearly 100% sensitivity
- ± CT to better characterize fractures



#### Ottawa Ankle Rules (see [Emergency Medicine, ER17](#))

X-rays are only required if:  
Pain in the malleolar zone AND bony tenderness over the posterior aspect of the medial or lateral malleolus OR inability to weight bear both immediately after injury and in the ER.



## Ankle Fracture

### Mechanism

- pattern of fracture depends on the position of the ankle when trauma occurs
- generally involves
  - ipsilateral ligamentous tears or transverse bony avulsion
  - contralateral shear fractures (oblique or spiral)
- classification systems
  - Danis-Weber (see below)
  - Lauge-Hansen: based on foot's position and motion relative to leg

### Danis-Weber Classification (Figure 47)

- based on level of fibular fracture relative to syndesmosis
- **Type A** (infra-syndesmotic)
  - pure inversion injury
  - avulsion of lateral malleolus below plafond or torn calcaneofibular ligament
  - ± shear fracture of medial malleolus
- **Type B** (trans-syndesmotic)
  - external rotation and eversion (most common)
  - ± avulsion of medial malleolus or rupture of deltoid ligament
  - spiral fracture of lateral malleolus starting at plafond
- **Type C** (supra-syndesmotic)
  - pure external rotation
  - avulsion of medial malleolus or torn deltoid ligament
  - ± posterior malleolus avulsion with posterior tibio-fibular ligament
  - fibular fracture is above plafond (called Maisonneuve fracture if at proximal fibula)
  - frequently tears syndesmosis

### Treatment

- undisplaced: non-weight bearing below knee cast
- indications for ORIF
  - any fracture-dislocation: restore vascularity, minimize articular injury, reduce pain and skin pressure
  - most of type B, and all of type C
  - trimalleolar (medial, posterior, lateral) fractures
  - talar tilt >10°
  - medial clear space on x-ray greater than superior clear space
  - open fracture/open joint injury
- high incidence of post-traumatic arthritis
- wrinkle test: skin shows wrinkles, to determine if soft tissue swelling has resolved to an extent to reduce complications

## Ligamentous Injuries

- see Figure 48 for ankle ligaments

### Medial Ligament Complex (deltoid ligament)

- eversion injury
- usually avulses medial or posterior malleolus and strains syndesmosis

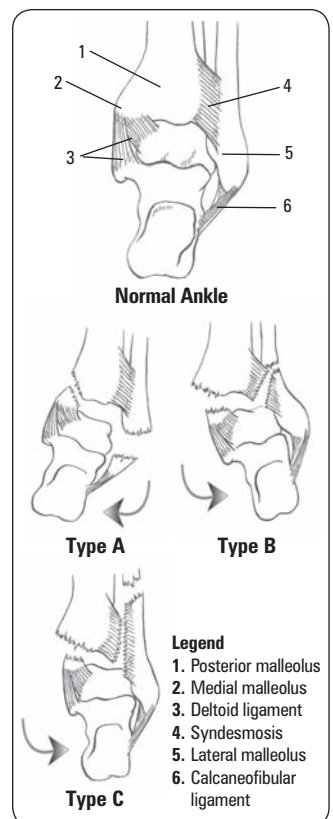


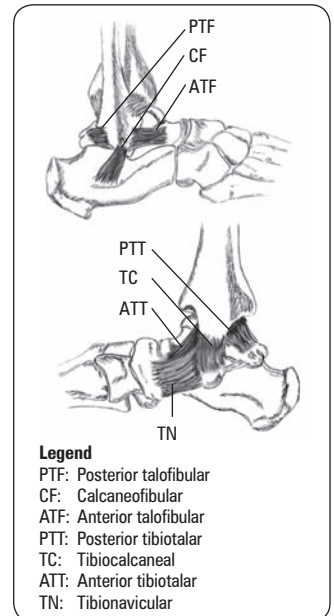
Figure 47. Ring principle of the ankle and Danis-Weber classification

**Lateral Ligament Complex (Anterior Talofibular, Calcaneofibular, Posterior Talofibular)**

- inversion injury
- ATF most commonly and severely injured if ankle is plantar flexed
- swelling and tenderness anterior to lateral malleolus
- ++ ecchymoses
- +ve ankle anterior drawer
- may have significant medial talar tilt on inversion stress x-ray

**Treatment**

- microscopic tear (Grade I)
  - rest, ice, compression, elevation (RICE)
- macroscopic tear (Grade II)
  - strap ankle in dorsiflexion and eversion x 4-6 wk
  - physiotherapy: strengthening and proprioceptive retraining
- complete tear (Grade III)
  - below knee walking cast x 4-6 wk
  - physiotherapy: strengthening and proprioceptive retraining
  - surgical intervention may be required if chronic symptomatic instability develops



**Figure 48. Ankle ligament complexes**



With a history of trauma from axial loading of lower limb always consider spinal injuries, femoral neck, tibial plateau, and talar/calcaneal fractures.



**Calcaneal Fracture Treatment Principles**

- Avoid wound complications
- Restore articular congruity
- Restore normal calcaneal width and height
- Maximum functional recovery may take longer than 12 mo

## Foot

### Talar Fracture

**Mechanism**

- axial loading or hyperdorsiflexion (MVC, fall from height)
- 60% of talus covered by articular cartilage
- tenuous blood supply runs distal to proximal along talar neck
  - high risk of AVN with displaced fractures

**Investigations**

- x-rays: AP, lateral
- CT to better characterize fracture
- MRI can clearly define extent of AVN

**Treatment**

- undisplaced: non-weight bearing below knee cast x 20-24 wk
- displaced: ORIF (high rate of nonunion, AVN)

### Calcaneal Fracture

**Mechanism**

- axial loading: fall from height onto heels
- 10% of fractures associated with compression fractures of thoracic or lumbar spine
- 5% are bilateral

**Physical Examination**

- swelling, bruising on heel/sole
- wider, shortened, flatter heel when viewed from behind
- varus heel

**Investigations**

- x-rays: AP, lateral, oblique (Broden's view)
- loss of Bohler's angle
- CT: assess intra-articular extension

**Treatment**

- closed vs. open reduction is controversial
- non-weight bearing cast x 3 mo with early ROM and strengthening

### Achilles Tendonitis

**Mechanism**

- chronic inflammation from activity or poor-fitting footwear
- may also develop heel bumps (retrocalcaneobursitis)

### Physical Examination

- pain, stiffness and crepitus with ROM
- thickened tendon, palpable bump

### Treatment

- rest, NSAIDs
- gentle stretching, deep tissue calf massage
- orthotics, open back shoes
- shockwave therapy in chronic tendonitis
- DO NOT inject steroids (risk of tendon rupture)

## Achilles Tendon Rupture

### Mechanism

- loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
- secondary to chronic tendonitis, steroid injection

### Clinical Features

- audible pop, sudden pain with push off movement
- sensation of being kicked in heel when trying to plantar flex
- palpable gap
- apprehensive toe off when walking
- weak plantar flexion strength
- Thompson test: with patient prone, squeezing the calf muscles should passively plantar flex the foot to demonstrate intact Achilles tendon
  - +ve test = no passive plantar flexion = ruptured tendon

### Treatment

- low demand or elderly: cast foot in plantar flexion (to relax tendon) x 8-12 wk
- high demand: surgical repair, then cast as above x 6-8 wk



#### Complications of Achilles Tendon Rupture

- Infection
- Sural nerve injury
- Rerupture: surgical repair decreases likelihood of rerupture compared to nonoperative management



The most common site of Achilles tendon rupture is 2-6 cm from its insertion where the blood supply is the poorest.

## Plantar Fasciitis (Heel Spur Syndrome)

### Mechanism

- repetitive strain injury causing microtears and inflammation of plantar fascia
- female:male = 2:1
- common in athletes (especially runners)
- also associated with obesity, DM, seronegative and seropositive arthritis

### Clinical Features

- morning pain and stiffness
- intense pain when walking from rest that subsides as patient continues to walk
- swelling, tenderness over sole
- greatest at medial calcaneal tubercle and 1-2 cm distal along plantar fascia
- pain with toe dorsiflexion (stretches fascia)

### Investigations

- plain radiographs to rule out fractures
- often see bony exostoses (heel spurs) at insertion of fascia into medial calcaneal tubercle (see Figure 49)
- spur is secondary to inflammation, not the cause of pain

### Treatment

- rest, ice, NSAIDs, steroid injection
- physiotherapy: stretching, ultrasound, extracorporeal shockwave therapy
- orthotics with heel cup
  - to counteract pronation and disperse heel strike forces
- endoscopic surgical release of fascia in refractory cases
  - spur removal is not required

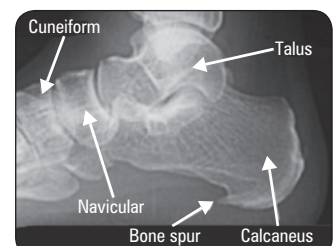


Figure 49. X-ray of bony heel spur

## Bunions (Hallux Valgus)

### Mechanism

- valgus alignment on 1st MTP (hallux valgus) causes eccentric pull of extensor and intrinsic muscles
- reactive exostosis forms with thickening of the skin creating a bunion
- most often associated with poor-fitting footwear but can be hereditary
- 10x more frequent in women

### Clinical Features

- painful bursa over medial eminence of 1st metatarsal head
- pronation (rotation inward) of great toe
- numbness over medial aspect of great toe

### Investigations

- x-ray: standing AP/lateral/sesamoid view, non-weight bearing oblique

### Treatment

- indications: painful corn or bunion, overriding 2nd toe
- non-operative first
  - properly fitted shoes (low heel) and toe spacer
- surgical: goal is to restore normal anatomy
  - osteotomy with realignment of 1st MTP joint (Chevron Procedure)
  - arthrodesis

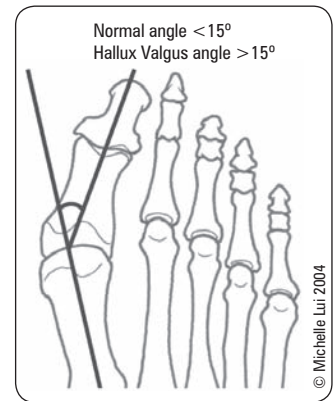


Figure 50. Hallux valgus

## Metatarsal Fracture

- as with the hand, 1st, 4th, 5th MT are relatively mobile, while the 2nd and 3rd are fixed (Table 22)
- use Ottawa Foot Rules to determine need for x-ray (see sidebar)

Table 22. Types of Metatarsal Fractures

Fracture Type	Mechanism	Clinical	Treatment
Avulsion of base of 5th MT	Sudden inversion followed by contraction of peroneus brevis	Tender base of 5th MT	Requires ORIF if displaced
Midshaft 5th MT (Jones fracture)	Stress injury	Painful shaft of 5th MT	*NWB BK cast x 6 wk ORIF if athlete
Shaft 2nd, 3rd MT (March fracture)	Stress injury	Painful shaft of 2nd or 3rd MT	Symptomatic
1st MT	Trauma	Painful 1st MT	ORIF if displaced otherwise NWB BK cast x 3 wk then walking cast x 2 wk
Tarso-MT fracture – dislocation (Lisfranc fracture)	Fall onto plantar flexed foot or direct crush injury	Shortened forefoot prominent base	ORIF

\*NWB BK = Non weight bearing, below knee



**Ottawa Ankle and Foot Rules**  
(see [Emergency Medicine, ER17](#))  
X-rays only required if:  
Pain in the midfoot zone AND bony tenderness over the navicular or base of the fifth metatarsal OR inability to weight bear both immediately after injury and in the ER.

## Pediatric Orthopedics

### Fractures in Children

- type of fracture
  - thicker, more active periosteum results in pediatric specific fractures: greenstick, torus (buckle) and plastic (bowing)
  - adults fracture through both cortices
- epiphyseal growth plate
  - weaker part of bone, susceptible to fractures
  - plate often mistaken for fracture on x-ray and vice versa (x-ray opposite limb for comparison), especially in elbow (see sidebar)
  - tensile strength of bone < ligaments in children, therefore clinician must be confident that fracture and/or growth plate injury have been ruled out before diagnosing a sprain
  - intra-articular fractures have worse consequences in children because they usually involve the growth plate
- anatomic reduction
  - gold standard with adults
  - may cause limb length discrepancy in children (overgrowth)
  - accept greater angular deformity in children (remodeling minimizes deformity)
- time to heal
  - shorter in children
- always be aware of the possibility of child abuse
  - make sure stated mechanism compatible with injury
  - high index of suspicion with fractures in non-ambulating children (<1 yr); look for other signs, including x-ray evidence of healing fractures at different sites and different stages of healing



Greenstick fractures are easy to reduce but can redisplace while in cast due to intact periosteum.

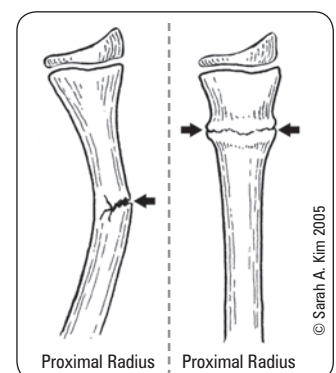


Figure 51. Greenstick (left) and torus (right) fractures



## Stress Fractures

### Mechanism

- insufficiency fracture
  - stress applied to a weak or structurally deficient bone
- fatigue fracture
  - repetitive, excessive force applied to normal bone
- most common in adolescent athletes
- tibia is most common site

### Diagnosis and Treatment

- localized pain and tenderness over the involved bone
- plain films may not show fracture for 2 wk
- bone scan +ve in 12-15 d
- treatment is rest from strenuous activities to allow remodeling (can take several months)

## Evaluation of the Limping Child

- see [Pediatrics](#), P96

## Epiphyseal Injury

**Table 23. Salter-Harris Classification of Epiphyseal Injury**

SALT(E)R-Harris Type	Description	Treatment
I (Straight through; Stable)	Transverse through growth plate	Closed reduction and cast immobilization (except SCFE – ORIF); heals well, 95% do not affect growth
II (Above)	Through metaphysis and along growth plate	Closed reduction and cast if anatomic; otherwise ORIF
III (Low)*	Through epiphysis to plate and along growth plate	Anatomic reduction by ORIF to prevent growth arrest, avoid fixation across growth plate
IV (Through and through)*	Through epiphysis and metaphysis	Closed reduction and cast if anatomic; otherwise ORIF
V (Ram)*	Crush injury of growth plate	High incidence of growth arrest; no specific treatment

\* Types III – IV are more likely to cause growth arrest and progressive deformity

## Slipped Capital Femoral Epiphysis (SCFE)

- type I Salter-Harris epiphyseal injury at proximal hip
- most common adolescent hip disorder, peak incidence at pubertal growth spurt
- risk factors: male, obese, hypothyroid

### Etiology

- multifactorial
  - genetic: autosomal dominant, blacks > caucasians
  - cartilaginous physis thickens rapidly under growth hormone effects
  - sex hormone secretion, which stabilizes physis, has not yet begun
  - overweight: mechanical stress
  - trauma: causes acute slip

### Clinical Features

- acute: sudden, severe pain with limp
- chronic: limp with medial knee or anterior thigh pain
  - +ve Trendelenburg sign on affected side, due to weakened gluteal muscles
- tender over joint capsule
- restricted internal rotation, abduction, flexion
  - Whitman's sign: with flexion there is an oblique external rotation of the hip
- pain at extremes of ROM

### Investigations

- x-rays: AP, frog-leg, lateral radiographs
  - posterior and medial slip
  - disruption of Klein's line (see sidebar)
  - AP view may be normal or show slightly widened growth plate compared with opposite side



### Ossification Centres of the Elbow

#### CRITOE

Capitellum: 1 yr

Radial head: 4 yr

Internal (medial) epicondyle: 6 yr

Trochlea: 8 yr

Olecranon: 10 yr

External (lateral) epicondyle: 12 yr  
(± 1 yr)

#### Type I



#### Type II



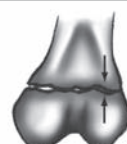
#### Type III



#### Type IV



#### Type V



© Kimberly Chin

**Figure 52. Salter-Harris classification**



In slipped capital femoral epiphysis, bilateral involvement occurs in about 25%.



### SCFE – Klein's Line

On AP view, line drawn along supero-lateral border of femoral neck should cross at least a portion of the femoral epiphysis. If it doesn't, suspect SCFE.

### Treatment and Complications

- mild/moderate slip: stabilize physis with pins in current position
- severe slip: ORIF or pin physis without reduction and osteotomy after epiphyseal fusion
- complications: AVN (most common), chondrolysis (loss of articular cartilage, resulting in narrowing of joint space), pin penetration, premature OA, loss of ROM

## Developmental Dysplasia of the Hip

- formerly called congenital dysplasia of the hip
- due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
- spectrum of conditions that lead to hip subluxation and dislocation
  - dislocated femoral head completely out of acetabulum
  - dislocatable head in socket
  - head subluxates out of joint when provoked
  - dysplastic acetabulum, more shallow and more vertical than normal
- painless (if painful suspect septic dislocation)

### Physical Examination

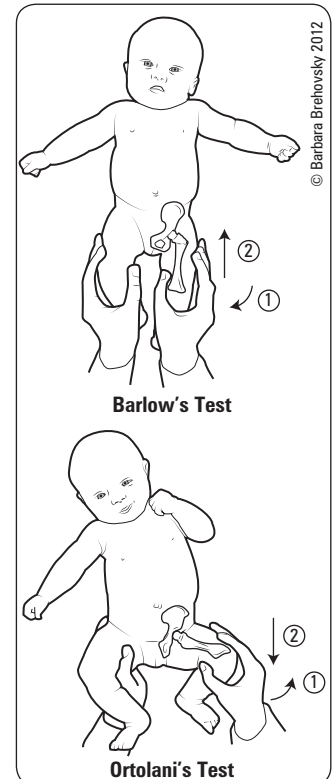
- diagnosis is clinical
  - limited abduction of the flexed hip (<50-60°)
  - affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
  - Barlow's test (for dislocatable hip)
    - ♦ flex hips and knees to 90° and grasp thigh
    - ♦ fully adduct hips, push posteriorly to try to dislocate hips
  - Ortolani's test (for dislocated hip)
    - ♦ initial position as above but try to reduce hip with fingertips during abduction
    - ♦ positive test: palpable clunk is felt (not heard) if hip is reduced
  - Galeazzi's sign
    - ♦ knees at unequal heights when hips and knees flexed
    - ♦ dislocated hip on side of lower knee
    - ♦ difficult test if child <1 yr
    - ♦ Trendelenburg test and gait useful if older (>2 yr)

### Investigations

- U/S in first few months to view cartilage (bone is not calcified in newborns)
- follow up radiograph after 3 mo
- x-ray signs: false acetabulum, acetabular index >30°, broken Shenton's line, femoral neck above Hilgenreiner's line, ossification centre outside of inner lower quadrant (quadrants formed by intersection of Hilgenreiner's and Perkin's line)

### Treatment and Complications

- 0-6 mo: reduce hip using Pavlik harness to maintain abduction and flexion
- 6-18 mo: reduction under GA, hip spica cast x 2-3 mo (if Pavlik harness fails)
- >18 mo: open reduction; pelvic and/or femoral osteotomy
- complications
  - redislocation, inadequate reduction, stiffness
  - AVN of femoral head



**Figure 53. Barlow's test** (checks if hips are dislocatable) **and Ortolani's test** (checks if hips are dislocated)



#### 5 Fs that Predispose to Developmental Dysplasia of the Hip

Family history  
Female  
Frank breech  
First born  
LeFt hip



Children diagnosed with coxa plana  
<6 yr of age have improved prognosis.

## Legg-Calvé-Perthes Disease (Coxa Plana)

- self-limited AVN of femoral head, presents at 4-10 yr of age
- etiology unknown, 20% bilateral, males > females, 1/10,000
- associations
  - family history
  - low birth weight
  - abnormal pregnancy/delivery
  - history of trauma to affected hip
- key features
  - AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodelling of regenerated bone

### Clinical Features

- child with hip pain and limp
- tender over anterior thigh
- flexion contracture: decreased internal rotation and abduction of hip

## Investigations

- x-rays
  - may be negative early (if high index of suspicion, move to bone scan or MRI)
  - eventually, characteristic collapse of femoral head (diagnostic)

## Treatment

- goal is to preserve ROM and preserve femoral head in acetabulum
- physiotherapy: ROM exercises
- brace in flexion and abduction x 2-3 yr
- femoral or pelvic osteotomy
  - prognosis better in males, <5 yr old, <50% of femoral head involved, abduction >30°
- 50% of involved hips do well with non-operative treatment
- complicated by early onset osteoarthritis and decreased ROM

## Osgood-Schlatter Disease

### Mechanism

- repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)

### Clinical Features

- tender lump over tibial tuberosity
- pain on resisted leg extension
- anterior knee pain exacerbated by jumping or kneeling, relieved by rest

### Investigations

- x-rays: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

### Treatment

- benign, self-limited condition
- may restrict activities such as basketball or cycling
- flexibility, isometric strengthening exercises



Most common in adolescent athletes, especially jumping sports.

## Congenital Talipes Equinovarus (Club Foot)

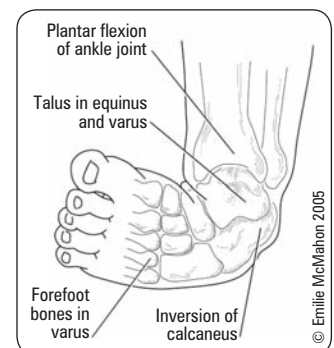
- etiology: intrinsic causes (neurologic, muscular, or connective tissue diseases) vs. extrinsic (intrauterine growth restriction), may be idiopathic, neurogenic, or syndrome-associated
- fixed deformity
- 3 parts to deformity
  - talipes: talus is inverted and internally rotated
  - equinus: ankle is plantar flexed
  - varus: heel and forefoot are in varus (supinated)
- 1-2/1,000 newborns, 50% bilateral, occurrence M>F, severity F>M

### Physical Examination

- examine hips for associated DDH
- examine knees for deformity
- examine back for dysraphism (unfused vertebral bodies)

### Treatment

- correct deformities in the following order (Ponseti Technique):
  - forefoot adduction, ankle inversion, equinus
    - ♦ change strapping/cast q1-2wk
  - surgical release in refractory case (rare)
    - ♦ delayed until 3-4 mo of age
- 3 yr recurrence rate = 5-10%
- mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf muscle atrophy



**Figure 54. The club foot – depicting the gross and bony deformity**

## Scoliosis

### Definition

- lateral curvature of spine with vertebral rotation

### Epidemiology

- age: 10-14 yr
- more frequent and more severe in females



Scoliosis screening is not recommended in Canada (Grieg A, et al. 2010; Health Canada, 1994).

### Etiology

- idiopathic: most common (90%)
- congenital: vertebrae fail to form or segment
- neuromuscular: UMN or LMN lesion, myopathy
- postural: leg length discrepancy, muscle spasm
- other: osteochondrodystrophies, neoplastic, traumatic

### Clinical Features

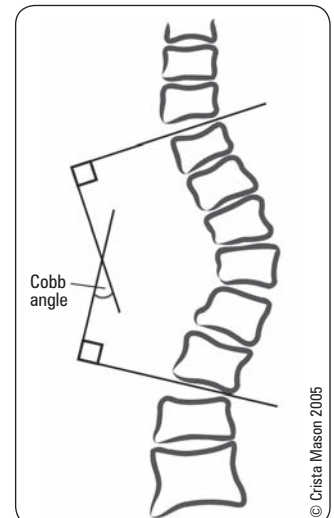
- $\pm$  back pain
- 1° curve where several vertebrae affected
- 2° curves above and below fixed 1° curve to try and maintain normal position of head and pelvis
- asymmetric shoulder height when bent forward
- Adam's test: rib hump when bent forward
- prominent scapulae, creased flank, asymmetric pelvis
- associated posterior midline skin lesions in neuromuscular scolioses
  - café-au-lait spots, dimples, neurofibromas
  - axillary freckling, hemangiomas, hair patches
- associated pes cavus or leg atrophy
- apparent leg length discrepancy

### X-Rays

- 3-foot standing, AP, lateral
  - measure curvature: Cobb angle (Figure 55)
  - may have associated kyphosis

### Treatment

- based on Cobb angle
  - $<20^\circ$ : observe for changes
  - $>20^\circ$  or progressive: bracing (many types) that halt/slow curve progression but do NOT reverse deformity
  - $>40^\circ$ , cosmetically unacceptable or respiratory problems: surgical correction (spinal fusion)



**Figure 55. Cobb angle** – used to monitor the progression of the scoliotic curve



In structural or fixed scoliosis, bending forwards makes the curve more obvious.

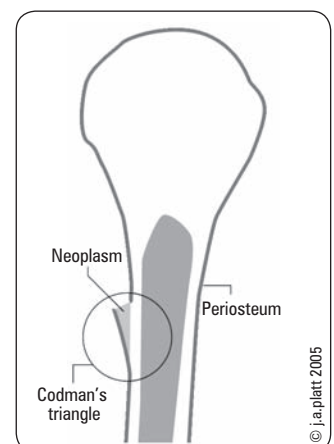


Postural scoliosis can be corrected by correcting the underlying problem.



#### Red Flags

- Persistent skeletal pain
- Localized tenderness
- Spontaneous fracture
- Enlarging mass/soft tissue swelling



**Figure 56. Codman's triangle** – a radiographic finding in malignancy, where the partially ossified periosteum is lifted off the cortex by neoplastic tissue

## Bone Tumours

- primary bone tumours are rare after 3rd decade
- metastases to bone are relatively common after 3rd decade

**Table 24. Distinguishing Benign from Malignant Bone Lesions on X-ray**

Benign	Malignant
No periosteal reaction	Acute periosteal reaction <ul style="list-style-type: none"> <li>• Codman's triangle</li> <li>• "Onion skin"</li> <li>• "Sunburst"</li> </ul>
Thick endosteal reaction	Broad border between lesion and normal bone
Well developed bone formation	Varied bone formation
Intraosseous and even calcification	Extrasosseous and irregular calcification

Adapted from: Buckholz RW and Heckman JD. Rockwood and Green's Fractures in Adults. Volume 1. Philadelphia: Lippincott Williams & Wilkins, 2001, 558

### Diagnosis

- pain, swelling, tenderness, rarely regional adenopathy
- routine x-ray findings
  - location (which bone, diaphysis, metaphysis, epiphysis)
  - size
  - lytic/lucent vs. sclerotic
  - involvement (cortex, medulla, soft tissue)
  - matrix (radiolucent, radiodense or calcified)
  - periosteal reaction
  - margin (geographic vs. permeative)
  - any pathological fracture
  - soft tissue swelling
- malignancy is suggested by rapid growth, warmth, tenderness, lack of sharp definition
- staging should include
  - bloodwork including liver enzymes
  - CT chest
  - bone scan
  - bone biopsy
    - ♦ should be referred to specialized centre prior to biopsy
    - ♦ classified into benign, benign aggressive, and malignant
  - MRI of affected bone

## Benign Active Bone Tumours

### BONE-FORMING TUMOURS

#### Osteoid Osteoma

- peak incidence in 2nd and 3rd decades, M:F = 3:1 (young males)
- tibia and femur most common locations
- not known to metastasize
- radiographic findings: small, round radiolucent nidus (<1 cm) surrounded by dense sclerotic bone ("bull's-eye")
- symptoms: produces severe intermittent pain, mostly at night (diurnal prostaglandin production), characteristically relieved by NSAIDs
- treatment: NSAIDs for night pain; surgical resection of nidus

### FIBROUS LESIONS

#### Fibrous Cortical Defect

- occur in as many as 35% of children, peak incidence between 2-20 yr old, higher prevalence in males
- femur and proximal tibia most common locations, 50% of patients have multiple defects usually bilateral, symmetrical
- radiographic findings: circular/oval, eccentric radiolucency near physis; thin smooth/lobulated well-defined sclerotic margin
- treatment: resolves spontaneously

#### Osteochondroma

- 2nd and 3rd decades, M:F = 1.8:1
- most common of all benign bone tumours – 45%
- metaphysis of long bone (usually distal femur, proximal tibia or proximal humerus)
  - radiographic findings: cartilage-capped bony spur on surface of bone ("mushroom" on x-ray)
  - may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
- generally very slow growing and asymptomatic unless impinging on neurovascular structure
  - growth usually ceases when skeletal maturity is reached
- malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)

#### Enchondroma (Figure 57)

- 2nd and 3rd decades
- 50% occur in the small tubular bones of the hand and foot; others in femur, humerus, ribs
- benign cartilaginous growth, develops in medullary cavity
  - single/multiple enlarged rarefied areas in tubular bones
  - lytic lesion with sharp margination and central calcification
- malignant degeneration to chondrosarcoma occurs in 1-2% (pain in absence of pathologic fracture is an important clue)
- not known to metastasize



Figure 57. T1 MRI of femoral enchondroma

### CYSTIC LESIONS

#### Unicameral/Solitary Bone Cyst

- most common cystic lesion
- children and young adults, peak incidence during first 2 decades, M:F = 2:1
- proximal humerus and femur most common
- symptoms: asymptomatic, or local pain; complete pathological fracture (50% presentations) or incidental detection
- radiographic findings: lytic translucent area on metaphyseal side of growth plate, cortex thinned/expanded; well defined lesion
- treatment: aspiration followed by steroid injection; curettage ± bone graft indicated if re-fracture likely



Figure 58. X-ray of aneurysmal bone cyst. Note the aggressive destruction of bone

## Benign Aggressive Bone Tumours

#### Giant Cell Tumours/Aneurysmal Bone Cyst/Osteoblastoma (Figure 58)

- affects patients of skeletal maturity, peak 3rd decade
- osteoblastoma: found in the distal femur, proximal tibia, distal radius, sacrum, tarsal bones, spinae
- giant cell tumour: pulmonary metastases in 3%
- aneurysmal bone cysts: either solid with fibrous/granular tissue, or blood-filled



- radiographic findings:
  - giant cell tumour: eccentric lytic lesions, in epiphyses adjacent to subchondral bone; may break through cortex; T2 MRI enhances fluid within lesion (hyper-intense signal)
  - aneurysmal bone cyst: expanded with honeycomb shape
  - osteoblastoma: often nonspecific; calcified central nidus with radiolucent halo and sclerosis
- symptoms: local tenderness and swelling, pain may be progressive (giant cell tumours), ± symptoms of nerve root compression (osteoblastoma)
- 15% recur within 2 yr of surgery

### Treatment

- intralesional curettage + bone graft or cement
- wide local excision of expendable bones

## Malignant Bone Tumours

**Table 25. Most Common Malignant Tumour Types for Age**

Age	Tumour
<1	Neuroblastoma
1-10	Ewing's of tubular bones
10-30	Osteosarcoma, Ewing's of flat bones
30-40	Reticulum cell sarcoma, fibrosarcoma, periosteal osteosarcoma, malignant giant cell tumour, lymphoma
>40	Metastatic carcinoma, multiple myeloma, chondrosarcoma

### Osteosarcoma (Figure 59)

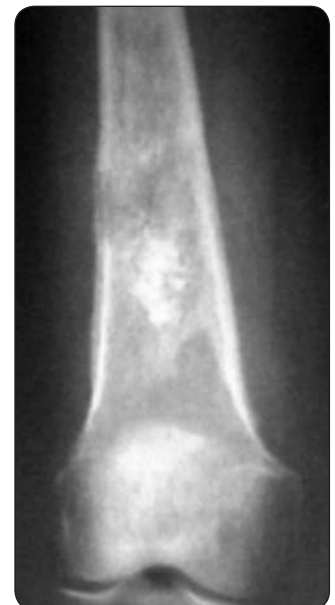
- most frequently diagnosed in 2nd decade of life (60%), 2nd most common primary malignancy in adults
- history of Paget's disease, previous radiation treatment
- predilection for sites of rapid growth: distal femur (45%), proximal tibia (20%), and proximal humerus (15%)
  - invasive, variable histology; frequent metastases without treatment (lung most common)
- painful symptoms: progressive pain, night pain, poorly defined swelling, decreased ROM
- radiographic findings:
  - characteristic periosteal reaction: Codman's triangle (Figure 56) or "sunburst" spicule formation (tumour extension into periosteum)
  - destructive lesion in metaphysis may cross epiphyseal plate
- management: complete resection (limb salvage, rarely amputation), neo-adjuvant chemo; bone scan – rule out skeletal metastases, CT chest – rule out pulmonary metastases
- prognosis: 70% (high-grade); 90% (low-grade)



**Figure 59. X-ray of osteosarcoma of distal femur**

### Chondrosarcoma (Figure 60)

- primary (2/3 cases)
  - previous normal bone, patient over 40; expands into cortex to give pain, pathological fracture, flecks of calcification
- secondary (1/3 cases)
  - malignant degeneration of pre-existing cartilage tumour such as enchondroma or osteochondroma
  - younger age group and better prognosis than primary chondrosarcoma
- symptoms: progressive pain, uncommonly palpable mass
- radiographic findings: in medullary cavity, irregular "popcorn" calcification
- treatment: unresponsive to chemotherapy, treat with aggressive surgical resection + reconstruction; regular follow-up x-rays of resection site and chest
- prognosis: 10-yr survival 90% low-grade, 20-40% high-grade



**Figure 60. X-ray of femoral chondrosarcoma**

### Ewing's Sarcoma

- most occur between 5-20 yr old
- florid periosteal reaction in metaphyses of long bone with diaphyseal extension
- metastases frequent without treatment
- signs/symptoms: presents with pain, mild fever, erythema and swelling, anemia, increased WBC, ESR, LDH
- radiographic findings: moth-eaten appearance with periosteal lamellated pattern ("onion-skinning")
- treatment: resection, chemotherapy, radiation
- prognosis – 70%, worst prognostic factor is distant metastases

### Multiple Myeloma

- most common primary malignant tumour of bone in adults (~43%)
- 90% occur in people >40 yr old, M:F = 2:1
- signs/symptoms: bone pain (cardinal early symptom), compression/pathological fractures, renal failure, nephritis, high incidence of infections (e.g. pyelonephritis/pneumonia), systemic (weakness, weight loss, anorexia)
- labs: anemia, thrombocytopenia, increased ESR, hypercalcemia



- radiographic findings: multiple, “punched-out” well-demarcated lesions, no surrounding sclerosis, marked bone expansion
- diagnosis:
  - serum/urine immunoelectrophoresis (monoclonal gammopathy)
  - CT-guided biopsy of lytic lesions at multiple bony sites
- treatment: chemotherapy, radiation, surgery for symptomatic lesions or impending fractures – debulking, internal fixation
- prognosis: most 3 yr after diagnosis
- see [Hematology](#), H47

### Bone Metastases

- 2/3 from breast or prostate; also consider thyroid, lung, kidney
- usually osteolytic; prostate occasionally osteoblastic
- bone scan for MSK involvement, MRI for spinal involvement may be helpful
- stabilization of impending fractures
  - internal fixation, IM rods
  - bone cement

**Table 26. Mirel's Criteria for Impending Fracture Risk and Prophylactic Internal Fixation**

Variable	Number Assigned		
	1	2	3
Site	Upper arm	Lower extremity	Peritrochanteric
Pain	Mild	Moderate	Severe
Lesion	Blastic	Mixed	Lytic
Size	<1/3 bone diameter	1/3-2/3 diameter	>2/3 diameter



#### Signs of Hypercalcemia

"Bones, Stones, Moans, Groans, Psychiatric overtones"

CNS: headache, confusion, irritability, blurred vision

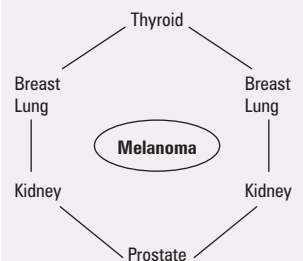
GI: N&V, abdominal pain, constipation, weight loss

MSK: fatigue, weakness, unsteady gait, bone and joint pain

GU: nocturia, polydipsia, polyuria, UTIs



#### Most Common Tumours Metastatic to Bone



#### BLT with a Kosher Pickle

Breast  
Lung  
Thyroid  
Kidney  
Prostate

## Common Medications

**Table 27. Common Medications**

Drug Name	Dosing Schedule	Indications	Comments
cefazolin (Ancef®)	1-2 g IV q8h	Prophylactically before orthopedic surgery	First generation cephalosporin; do not use with penicillin allergy
heparin	5000 IU SC q12h	To prevent venous thrombosis and pulmonary emboli	Monitor platelets, follow PTT which should rise 1.5-2x
LMWH			
dalteparin (Fragmin®)	5000 IU SC OD	DVT prophylaxis esp. in hip and knee surgery	Fixed dose, no monitoring, improved bioavailability, increased bleeding rates
enoxaparin (Lovenox®)	30-40 mg SC bid		
fondaparinux (Arixtra®)	2.5 mg SC OD		
midazolam (Versed®)	0.02 mg/kg IV	Conscious sedation for short procedures	Medication used during fracture reduction – monitor for respiratory depression
fentanyl (Sublimaze®)	0.5-3 µg/kg IV	Conscious sedation for short procedures	Short acting anesthetic used in conjunction with midazolam (Versed®)
triamcinolone (Aristocort®) – an injectable steroid	0.5-1 mL of 25 mg/mL	Suspension (injected into inflamed joint or bursa)	Potent anti-inflammatory effect; increased pain for 24 h, rarely causes fat necrosis and skin depigmentation
naproxen (Aleve®, Naprosyn®)	250-500 mg bid	Pain due to inflammation, arthritis, soft tissue injury	NSAID, may cause gastric erosion and bleeding
misoprostol (Cytotec®)	200 µg qid	Prophylaxis of heterotopic ossification after THA	Use with indomethacin
indomethacin (Indocid®)	25 mg PO tid	Prophylaxis of heterotopic ossification after THA	Use with misoprostol
ibuprofen (Advil®, Motrin®)	200-400 mg tid	Pain (including post-op), inflammation (including arthritis)	NSAID, may cause gastric erosion and bleeding
propofol (Diprivan®)	1-2 mg/kg IV Maint. 0.5 mg/kg	Conscious sedation for short procedures	Short acting anesthetic often used in conjunction with fentanyl (Sublimaze®)

# References

## Textbooks

- Adams JC, Hamblen DL. Outline of fractures: including joint injuries. 11th ed. Toronto: Churchill Livingstone, 1999.
- Blackbourne LH. LH Blackbourne (editor). Surgical recall. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2002.
- Brinker MR. Review of orthopedic trauma. Toronto: WB Saunders, 2001.
- Brinker M, Miller M. Fundamentals of orthopedics. Philadelphia: WB Saunders, 1999.
- Canale, ST. Campbell's operative orthopedics: volume 1, 10th ed. Philadelphia: Mosby, 2003. p733-855.
- Dee R, Hurst LC, Gruber MA, Kottmeier SA, editors. Principles of orthopedic practice, 2nd ed. Toronto: McGraw-Hill, 1997.
- Goldbloom RB. Screening for idiopathic adolescent scoliosis. Ottawa: Health Canada. Canadian Task Force on the Periodic Health Examination, Canadian Guide to Clinical Preventive Health Care, 1994. p346-353.
- Kao LD. Pre-test surgery. Toronto: McGraw-Hill, 2002.
- Magee DJ. Orthopedic physical assessment, 5th ed. St. Louis: WB Saunders Elsevier, 2008.
- Ochiai DH. The orthopedic intern pocket survival guide. McLean: International Medical Publishing, 2007.
- Rockwood CA Jr, Greene DP, Bucholz RU, Heckman JD, editors. Rockwood and Green's fractures in adults, 4th ed. Philadelphia: Lippincott Raven, 1996.
- Skinner HB. Current diagnosis and treatment in orthopedics, 4th ed. New York: McGraw-Hill, 2006.
- Solomon L, Warwick DJ, Nayagam, S. Apley's system of orthopedics and fractures, 8th ed. New York: Hodder Arnold, 2001.
- Thompson JC. Netter's concise atlas of orthopedic Anatomy. USA: Elsevier, 2001.
- Wong M. Pocket orthopedics: evidence-based survival guide. Sudbury: Jones and Bartlett Publishers, 2010.
- Zhang Y. Clinical Epidemiology of Orthopedic Trauma. New York: Thieme Medical Publishers, 2012.

## Journal Articles

- AAOS. The treatment of distal radius fractures: summary of recommendations (internet). 2009 (accessed June 5, 2011). Available from: <http://www.aaos.org/research/guidelines/DRFguideline.asp>.
- Adkins SB. Hip pain in athletes. Am Fam Phys 2000;61:2109-2118.
- Armagan OE, Shereff MJ. Injuries of the toes and metatarsals. Orthop Clin North Am 2001;32:1-10.
- Bareil DP, Bellabarba C, Sangeorzan BJ, Benirschke SK. Fractures of the calcaneus. Orthop Clin North Am 2001;33:263-285.
- Barrett SL. Plantar fasciitis and other causes of heel pain. Am Fam Phys 1999;59:2200-2206.
- Brand DA, Frazier WH, Kohlhepp WC, et al. A protocol for selecting patients with injured extremities who need x-rays. NEJM 1982;306:833-839.
- Canadian CT Head and C-Spine (CCC) Study Group. Canadian c-spine rule study for alert and stable trauma patients: background and rationale. CJEM 2002;4:84-90.
- Carek PJ. Diagnosis and management of osteomyelitis. Am Fam Phys 2001;63:2413-2420.
- Donatto KC. Ankle fractures and syndesmosis injuries. Orthop Clin North Am 2001;32:79-90.
- Fernandez M. Discitis and vertebral osteomyelitis in children: an 18-year review. Pediatrics 105:1299-1304.
- Fortin PT. Talus fractures: evaluation and treatment. J Am Acad Orthop Surg 2001;9:114-127.
- French B, Tornetta III P. High energy tibial shaft fractures. Orthop Clin North Am 2002;33:211-230.
- Gable, H Nunn, D. Image Interpretation Course. 2009, (accessed May 18, 2010). Available from: <http://www.imageinterpretation.co.uk>.
- Geerts WH, Heit JA, Clagett, GP, et al. Prevention of venous thromboembolism. Chest 2001;119(1 Suppl):132S-175S.
- Gosselin RA, Roberts I, Gillespie WJ. Antibiotics for preventing infection in open limb fractures. Cochrane DB Syst Rev.2004;1:CD003764.
- Greig A, Constantine E, Carsley S, et al. Preventive health care visits for children and adolescents aged six to 17 years: the Greig health record – executive summary. Ped Child Health 2010;15:157-159.
- Grover R. Clinical assessment of scaphoid injuries and the detection of fractures. J Hand Surg Br 1996;21:341-343.
- Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma 1984;24:742-746.
- Hamilton H, McIntosh G, Boyle C. Effectiveness of a low back classification system. Spine J 2009;9:648-657.
- Harty MP. Imaging of pediatric foot disorders. Radiol Clin North Am 2001;39:733-748.
- Irrgang JJ. Rehabilitation of multiple ligament injured knee. Clin Sports Med 2000;19:545-571.
- Karachalios T, et al. Diagnostic accuracy of a new clinical test (the Thessaly test) for early detection of meniscal tears. J Bone Joint Surg Am 2005;87:955-962.
- Lawrence LL. The limping child. Emerg Med Clin North Am 1998;169:911-929.
- Litaker, D, Piro M, El Bilbeisi H, Brems J. Returning to the bedside: using the history and physical examination to identify rotator cuff tears. J Am Geriatr Soc 2000;48:1633-1637.
- Lo IKNB, Woolfrey M, Litchfield R, Kirkey A. An evaluation of the apprehension, relocation, and surprise tests for anterior shoulder instability. American Journal of Sports Medicine. 2004;32:301-7.
- Luime JJ, Verhaagen AP, Miedema HS, Kuiper JI, Burdorf A, Verhaar JAN, Koes BW. An evaluation of the apprehension, relocation, and surprise tests for anterior shoulder instability. Am J Sports Med 2004;32:301-307.
- Mathews CJ, Coakley G. Septic arthritis: current diagnostic and therapeutic algorithm. Curr Opin Rheumatol 2008;20:457-462.
- Margaretten ME, Kohlwees J, Moore D, Bent S. Does this adult patient have septic arthritis? JAMA 2007;297:1478-1488.
- Mazzone MF. Common conditions of the achilles tendon. Am Fam Phys 2000;65:1805-1810.
- Murrell GA, Walton JR. Diagnosis of rotator cuff tears. Lancet 2001;357:769-770.
- Steele PM, Bush-Joseph C, Bach Jr B. Management of acute fractures around the knee, ankle, and foot. Clin Fam Pract 2000;2:661-705.
- Miller SL. Malignant and benign bone tumours. Radiol Clin North Am 2000;39:673-699.
- Okike K, Bhattacharyya T. Trends in the management of open fractures: a critical analysis. J Bone Joint Surg Am 2006;88:2739-2748.
- Oudjhane K. Imaging of osteomyelitis in children. Radiol Clin North Am 2001;39:251-266.
- Patel DR. Sports injuries in adolescents. Med Clin North Am 2000;84:983-1007.
- Roberts DM, Stallard TC. Emergency department evaluation and treatment of knee and leg injuries. Emerg Med Clin North Am 2000;18:67-84.
- Rockwood CA, Williams GR, Young DC. Disorders of the acromioclavicular joint. Rockwood CA, Masten FA II (editors). The shoulder. Philadelphia: Saunders, 1998. p483-553.
- Russell GV Jr. Complicated femoral shaft fractures. Orthop Clin North Am 2002;33:127-142.
- Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL. The rational clinical examination: does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. JAMA 2001;286:1610-1620.
- St Pierre P. Posterior cruciate ligament injuries. Clin Sports Med 1999;18:199-221.
- Steele PM, Bush-Joseph C, Bach Jr B. Management of acute fractures around the knee, ankle, and foot. Clin Fam Pract 2000;2:661-705.
- Stewart DG, Kay RM, Skaggs DL. Open fractures in children. Principles of evaluation and management. JBJS Am 2005;87:2784-2798.
- Swenson TM. The dislocated knee: physical diagnosis of the multiple-ligament-injured knee. Clin Sports Med 2000;19:415-423.
- Zollinger PE, Tuinbreijer WE, Kreis RW, Breederveld RS. Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: a randomized trial. Lancet 1999;354:2025-2058.

Peter Dixon and Ryan Figueroa, chapter editors

Jieun Kim and Daniel Soong, associate editors

Jeff Martin, EBM editor

Dr. Jonathan C. Irish and Dr. Evan J. Propst, staff editors

<b>Acronyms</b> .....	<b>2</b>	<b>Facial Nerve (CN VII) Paralysis</b> .....	<b>21</b>
<b>Basic Anatomy Review</b> .....	<b>2</b>	<b>Rhinitis</b> .....	<b>22</b>
Ear		Allergic Rhinitis (Hay Fever)	
Nose		Vasomotor Rhinitis	
Throat		<b>Rhinosinusitis</b> .....	<b>24</b>
Head and Neck		Acute Bacterial Rhinosinusitis	
Anatomical Triangles of the Neck		Chronic Rhinosinusitis	
<b>Differential Diagnoses of Common Presenting Problems</b> .....	<b>5</b>	<b>Epistaxis</b> .....	<b>26</b>
Dizziness		<b>Hoarseness</b> .....	<b>27</b>
Otalgia		Acute Laryngitis	
Hearing Loss		Chronic Laryngitis	
Tinnitus		Vocal Cord Polyps	
Nasal Obstruction		Vocal Cord Nodules	
Hoarseness		Benign Laryngeal Papillomas	
Neck Mass		Laryngeal Carcinoma	
<b>Hearing</b> .....	<b>9</b>	<b>Salivary Glands</b> .....	<b>29</b>
Normal Hearing Physiology		Sialadenitis	
Types of Hearing Loss		Sialolithiasis	
Pure Tone Audiometry		Salivary Gland Neoplasms	
Speech Audiometry		Parotid Gland Neoplasms	
Impedance Audiometry		<b>Neck Masses</b> .....	<b>31</b>
Auditory Brainstem Response		Approach to a Neck Mass	
Otoacoustic Emissions		Evaluation	
Aural Rehabilitation		<b>Congenital Neck Masses</b> .....	<b>32</b>
<b>Vertigo</b> .....	<b>12</b>	Branchial Cleft Cysts/Fistula	
Evaluation of the Dizzy Patient		Thyroglossal Duct Cysts	
Benign Paroxysmal Positional Vertigo		Lymphatic Malformation	
Menière's Disease (Endolymphatic Hydrops)		<b>Neoplasms of the Head and Neck</b> .....	<b>34</b>
Vestibular Neuronitis		Thyroid Carcinoma	
Labyrinthitis		<b>Pediatric Otolaryngology</b> .....	<b>38</b>
Acoustic Neuroma (Vestibular Schwannoma)		Acute Otitis Media (AOM)	
<b>Tinnitus</b> .....	<b>15</b>	Otitis Media with Effusion (OME)	
<b>Diseases of the External Ear</b> .....	<b>15</b>	Adenoid Hypertrophy	
Cerumen Impaction		Adenoidectomy	
Exostoses		Sleep-Disordered Breathing in Children	
Otitis Externa (OE)		Acute Tonsillitis	
Malignant (Necrotizing) Otitis Externa		Peritonsillar Abscess (Quinsy)	
(Skull Base Osteomyelitis)		Tonsillectomy	
<b>Diseases of the Middle Ear</b> .....	<b>17</b>	Airway Problems in Children	
Acute Otitis Media and Otitis Media with Effusion		Signs of Airway Obstruction	
Cholesteatoma		Acute Laryngotracheobronchitis (Croup)	
Mastoiditis		Acute Epiglottitis	
Otosclerosis		Subglottic Stenosis	
<b>Diseases of the Inner Ear</b> .....	<b>18</b>	Laryngomalacia	
Congenital Sensorineural Hearing Loss		Foreign Body	
Presbycusis		Deep Neck Space Infection	
Sudden Sensorineural Hearing Loss		<b>Common Medications</b> .....	<b>47</b>
Autoimmune Inner Ear Disease		<b>References</b> .....	<b>48</b>
Drug Ototoxicity			
Noise-Induced Sensorineural Hearing Loss			
Temporal Bone Fractures			

## Acronyms

ABR	auditory brainstem response	FAP	familial adenomatous polyposis	OSA	obstructive sleep apnea
AC	air conduction	FESS	functional endoscopic sinus surgery	RA	rheumatoid arthritis
AOM	acute otitis media	FNA	fine needle aspiration	SCC	squamous cell carcinoma
BAHA	bone anchored hearing aid	GERD	gastroesophageal reflux disease	SCM	sternocleidomastoid
BC	bone conduction	HL	hearing loss	SNHL	sensorineural hearing loss
CHL	conductive hearing loss	HPV	human papilloma virus	TEF	tracheoesophageal fistula
CPA	cerebellopontine angle	INCS	intranasal corticosteroids	TM	tympanic membrane
EAC	external auditory canal	OE	otitis externa	TNM	tumour, node, metastases
EBV	Epstein-Barr virus	OME	otitis media with effusion	URTI	upper respiratory tract infection

## Basic Anatomy Review

### Ear

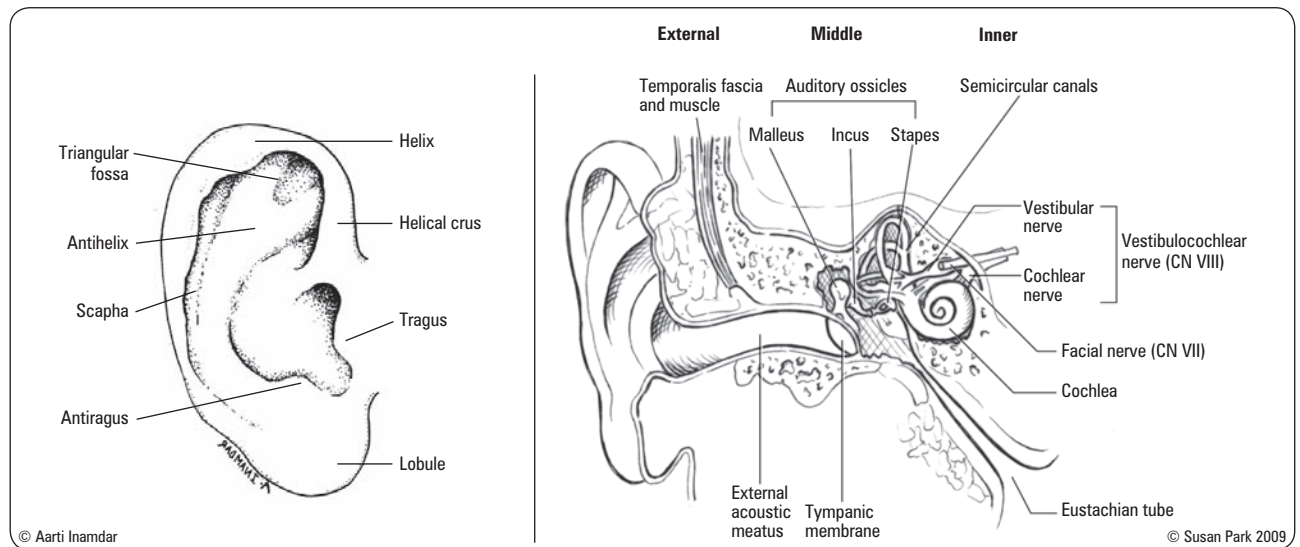


Figure 1. Surface anatomy of the external ear; anatomy of ear

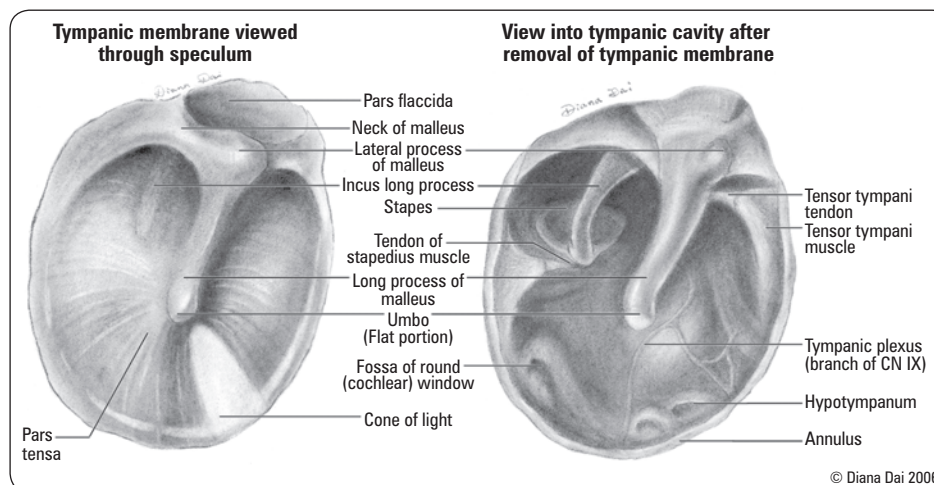


Figure 2. Normal appearance of right tympanic membrane on otoscopy

## Nose

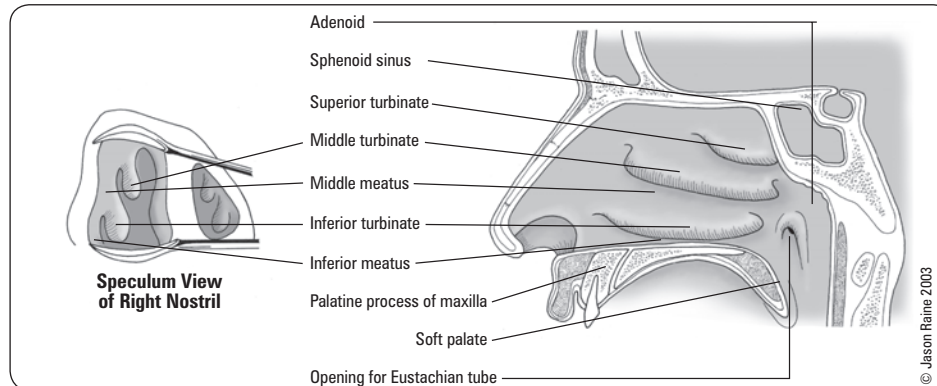


Figure 3. Nasal anatomy

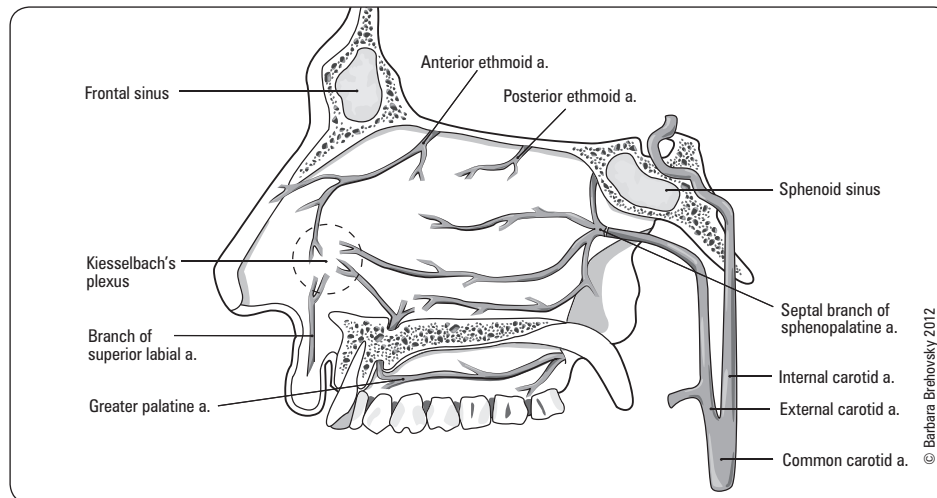


Figure 4. Nasal septum and its arterial supply (see *Epistaxis* section for detailed blood supply)

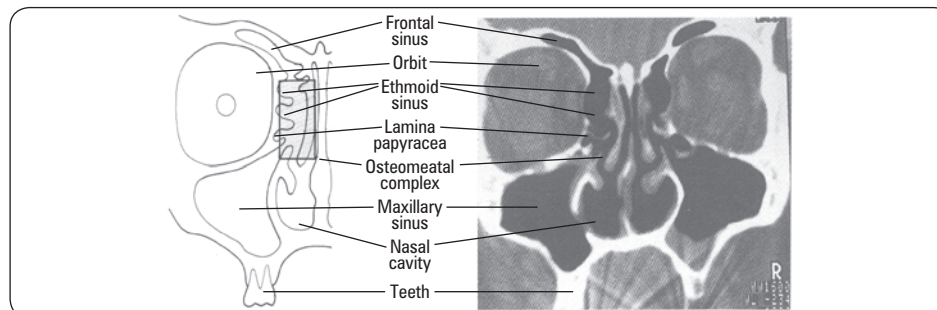


Figure 5. Anatomy of the four paranasal sinuses: maxillary, ethmoid, sphenoid, and frontal

Reprinted from Dhillon R.S, and East C.A. *Ear, Nose and Throat and Head and Neck Surgery*, 2nd ed. Copyright 1999, with permission from Elsevier.

## Throat

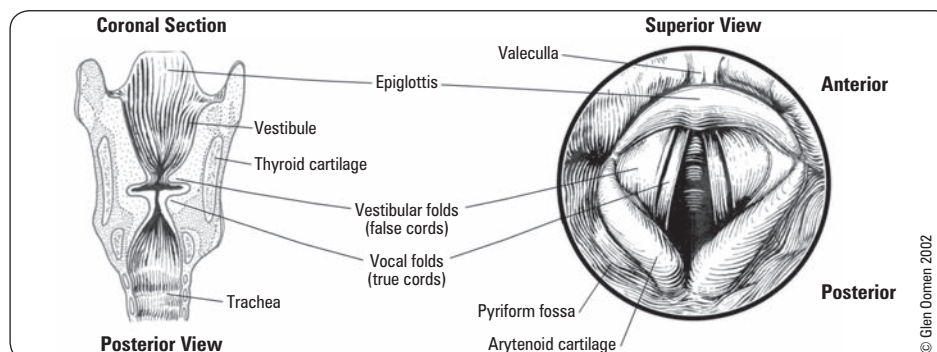


Figure 6. Anatomy of a normal larynx; superior view of larynx on indirect laryngoscopy



### Drainage into Nasal Cavity

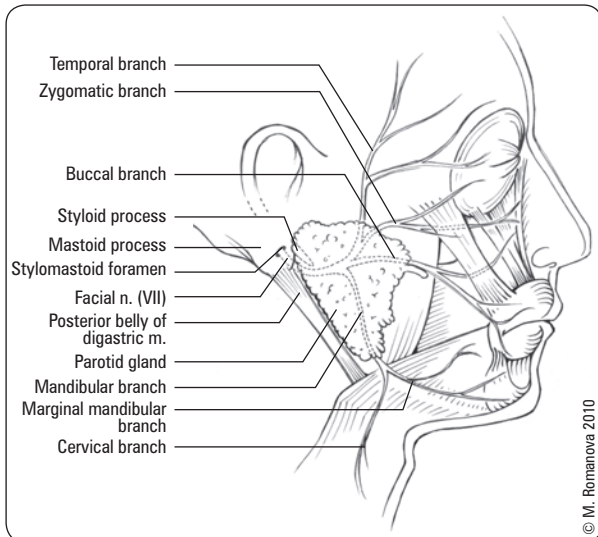
- **Superior meatus:** sphenoid (via sphenothmoidal recess), posterior ethmoid sinuses
- **Middle meatus:** frontal, maxillary, anterior ethmoid sinuses
- **Inferior meatus:** nasolacrimal duct



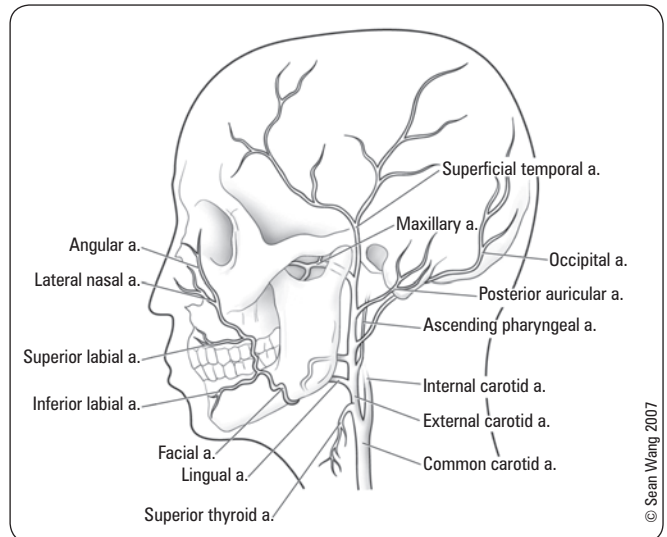
- **Nasopharynx:** skull base to soft palate
- **Oropharynx:** soft palate to hyoid bone
- **Laryngopharynx:** hyoid bone to inferior cricoid cartilage



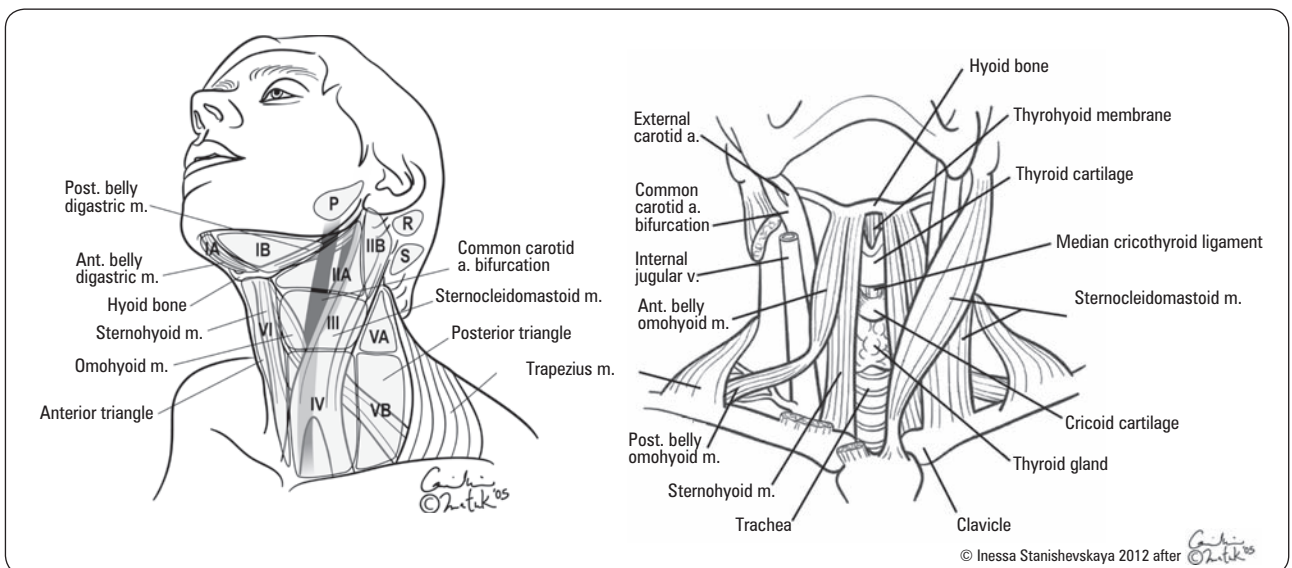
## Head and Neck



**Figure 7. Extratemporal segment of facial nerve**  
Branches of facial nerve (in order from superior to inferior)  
Ten Zebras Broke My Car



**Figure 8. Blood supply to the face**  
Branches of the external carotid artery (in order from inferior to superior)  
Some Angry Lady Figured Out PMS



**Figure 9. Anatomy of the neck**

## Anatomical Triangles of the Neck

### Anterior triangle:

- bounded by anterior border of SCM, midline of neck, and lower border of mandible
- divided into:
  - **submental triangle:** bounded by both anterior bellies of digastric and hyoid bone
  - **digastric triangle:** bounded by anterior and posterior bellies of digastric, and inferior border of mandible
  - **carotid triangle:** bounded by sternocleidomastoid, anterior belly of omohyoid, and posterior belly of digastric
    - ♦ contains: tail of parotid, submandibular gland, hypoglossal nerve, carotid bifurcation, and lymph nodes

### Posterior triangle:

- bounded by posterior border of sternocleidomastoid, anterior border of trapezius, and middle third of clavicle
- divided into:
  - **occipital triangle:** superior to posterior belly of the omohyoid
  - **subclavian triangle:** inferior to posterior belly of omohyoid
- contains: spinal accessory nerve and lymph nodes



### Paired Parasympathetic Ganglia of the Head and Neck

- **Ciliary:** pupillary constriction
- **Pterygopalatine:** lacrimal gland, nasal mucosa
- **Submandibular:** submandibular, sublingual glands
- **Otic:** parotid gland



### Function of Facial Nerve

#### "Ears, Tears, Face, Taste"

**Ears:** stapedius muscle

**Tears:** lacrimation (lacrimal gland) and salivation (parotid)

**Face:** muscles of facial expression

**Taste:** sensory anterior 2/3 of tongue (via chorda tympani)



**Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of Neck**

Nodal Group/Level	Location	Drainage
1. Suboccipital (S)	Base of skull, posterior	Posterior scalp
2. Retroauricular (R)	Superficial to mastoid process	Scalp, temporal region, external auditory meatus, posterior pinna
3. Parotid-preauricular (P)	In front of ear	External auditory meatus, anterior pinna, soft tissue of frontal and temporal regions, root of nose, eyelids, palpebral conjunctiva
4. Submental (Level IA)	(Midline) Anterior bellies of digastric muscles, tip of mandible, and hyoid bone	Floor of mouth, anterior oral tongue, anterior mandibular alveolar ridge, lower lip
5. Submandibular (Level IB)	Anterior belly of digastric muscle, stylohyoid muscle, body of mandible	Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland
6. Upper jugular (Levels IIA and IIB)	Skull base to inferior border of hyoid bone along SCM muscle	Oral cavity, nasal cavity, naso/oro/hypopharynx, larynx, parotid glands
7. Middle jugular (Level III)	Inferior border of hyoid bone to inferior border of cricoid cartilage along SCM muscle	Oral cavity, naso/oro/hypopharynx, larynx
8. Lower jugular* (Level IV)	Inferior border of cricoid cartilage to clavicle along SCM muscle	Hypopharynx, thyroid, cervical esophagus, larynx
9. Posterior triangle** (Levels VA and VB)	Posterior border of SCM, anterior border of trapezius, from skull base to clavicle	Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck
10. Anterior compartment*** (Level VI)	(Midline) Hyoid bone to suprasternal notch between the common carotid arteries	Thyroid gland, glottic and subglottic larynx, apex of piriform sinus, cervical esophagus

\*Virchow node: left lower level IV supraclavicular node

\*\*Includes some supraclavicular nodes

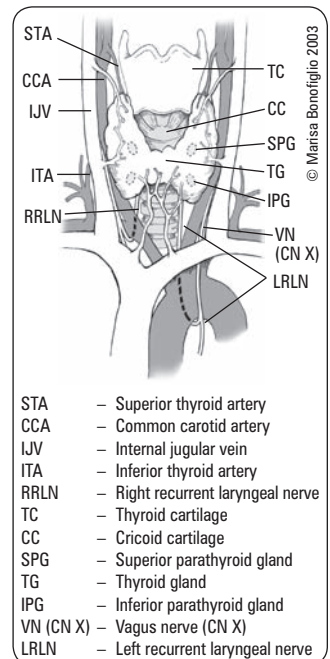
\*\*\*Includes pretracheal, precricoid, paratracheal, and perithyroidal nodes



- **Left-sided** enlargement of a supraclavicular node (Virchow's node) may indicate an abdominal malignancy
- **Right-sided** enlargement may indicate malignancy of the mediastinum, lungs, or esophagus
- **Occipital and/or posterior auricular node** enlargement may indicate rubella

**4 Strap Muscles of the Neck**

- Thyrohyoid
- Omohyoid
- Sternothyroid
- Sternohyoid



- STA – Superior thyroid artery  
 CCA – Common carotid artery  
 IJV – Internal jugular vein  
 ITA – Inferior thyroid artery  
 RRLN – Right recurrent laryngeal nerve  
 TC – Thyroid cartilage  
 CC – Cricoid cartilage  
 SPG – Superior parathyroid gland  
 TG – Thyroid gland  
 IPG – Inferior parathyroid gland  
 VN (CN X) – Vagus nerve (CN X)  
 LRLN – Left recurrent laryngeal nerve

**Figure 10. Anatomy of the thyroid gland**

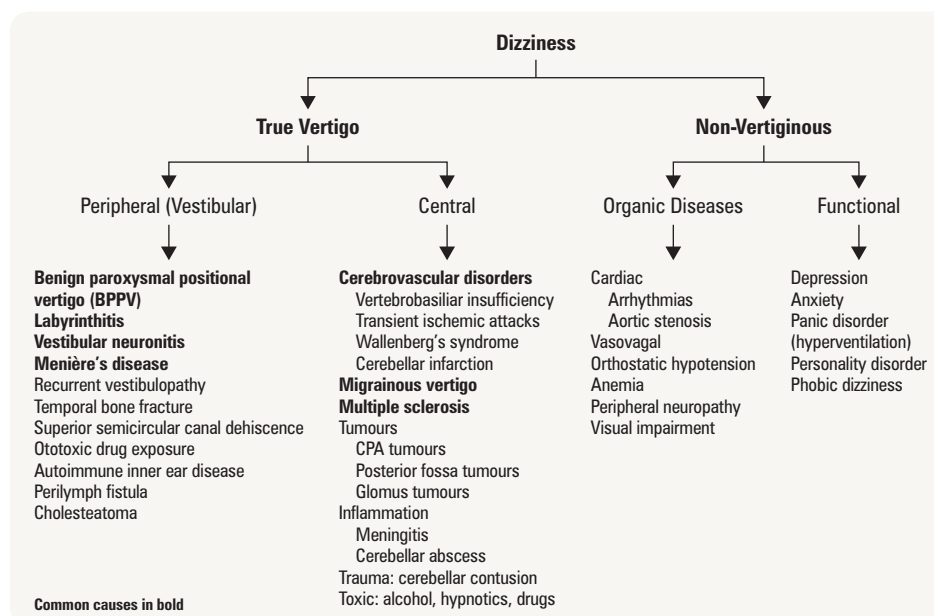
True nystagmus and vertigo caused by a peripheral lesion will never last longer than a couple of weeks because of compensation. Central lesions do not compensate, hence nystagmus and vertigo will persist.

**5 Ds of Vertebrobasilar Insufficiency**

- Drop attacks
- Diplopia
- Dysarthria
- Dizziness
- Dysphagia

## Differential Diagnoses of Common Presenting Problems

### Dizziness

**Figure 11. Differential diagnosis of dizziness**



## Otalgia

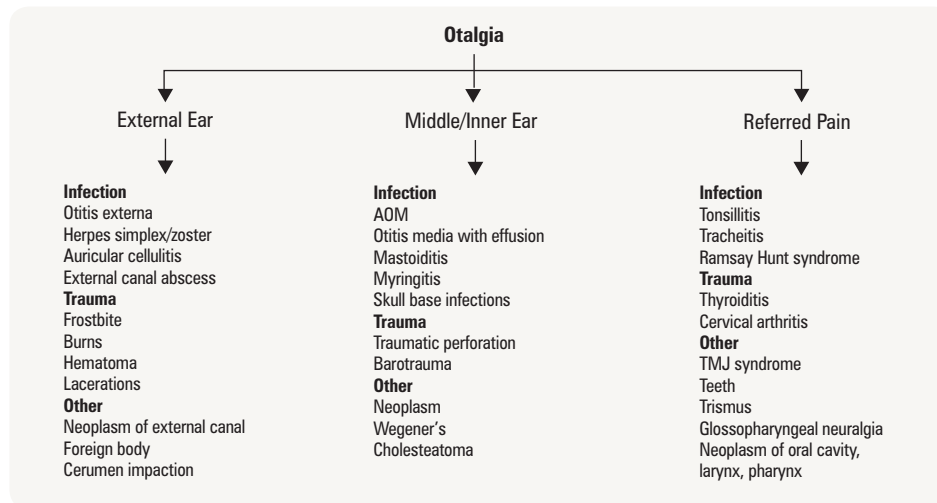


Figure 12. Differential diagnosis of otalgia

## Hearing Loss

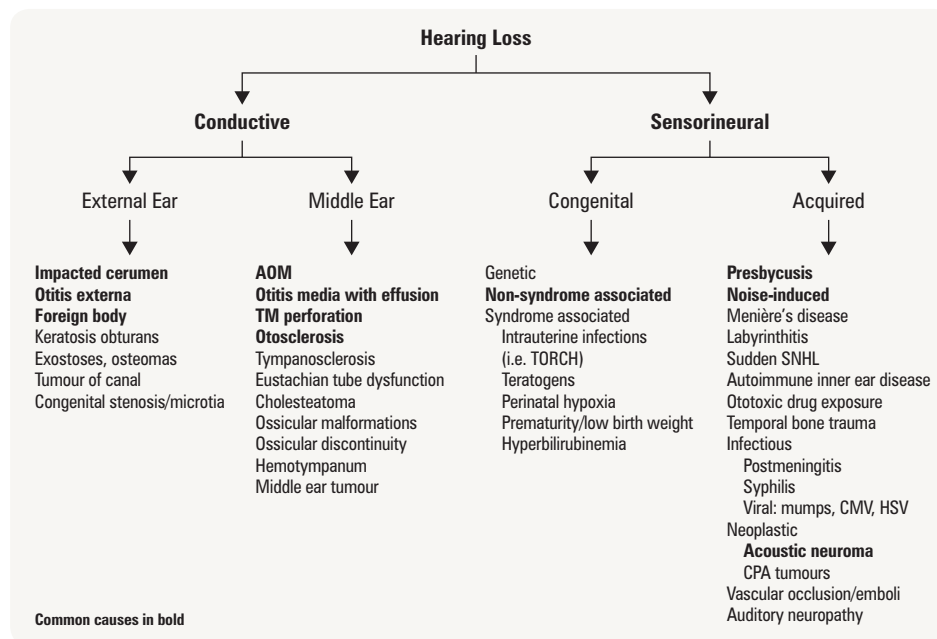
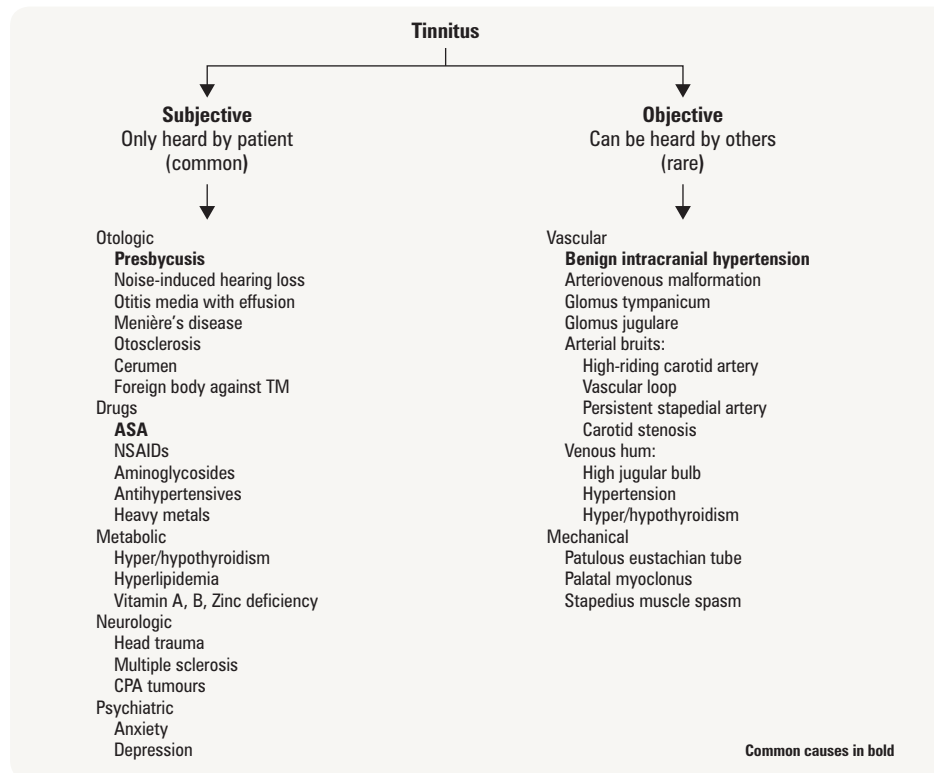


Figure 13. Differential diagnosis of hearing loss

## Tinnitus



Tinnitus is most commonly associated with SNHL.



**Glomus Tympanicum/Jugulare Tumour**  
**Signs and Symptoms**

- Pulsatile tinnitus
- Hearing loss
- Blue mass behind TM
- Brown's sign (blanching of the TM with pneumatic otoscopy)

Figure 14. Differential diagnosis of tinnitus

## Nasal Obstruction



Table 2. Differential Diagnosis of Nasal Obstruction

Acquired	Congenital
<b>Nasal Cavity</b> <ul style="list-style-type: none"> <li>Rhinitis               <ul style="list-style-type: none"> <li>Acute/chronic</li> <li>Vasomotor</li> <li>Allergic</li> </ul> </li> <li>Rhinosinusitis</li> <li>Foreign bodies</li> <li>Enlarged turbinates</li> <li>Tumour               <ul style="list-style-type: none"> <li>Benign: polyps, inverting papilloma</li> <li>Malignant                   <ul style="list-style-type: none"> <li>SCC</li> <li>Esthesioneuroblastoma (olfactory neuroblastoma)</li> <li>Adenocarcinoma</li> </ul> </li> </ul> </li> </ul>	<b>Nasal Cavity</b> <ul style="list-style-type: none"> <li>Nasal dermoid cyst</li> <li>Encephalocele</li> <li>Glioma</li> <li>Choanal atresia</li> </ul>
<b>Nasal Septum</b> <ul style="list-style-type: none"> <li>Septal deviation</li> <li>Septal hematoma/abscess</li> <li>Dislocated septum</li> </ul>	<b>Nasal Septum</b> <ul style="list-style-type: none"> <li>Septal deviation</li> <li>Septal hematoma/abscess</li> <li>Dislocated septum</li> </ul>
<b>Nasopharynx</b> <ul style="list-style-type: none"> <li>Adenoid hypertrophy</li> <li>Tumour               <ul style="list-style-type: none"> <li>Benign: juvenile nasopharyngeal angiofibroma (JNA), polyps</li> <li>Malignant: nasopharyngeal carcinoma</li> </ul> </li> </ul>	
<b>Systemic</b> <ul style="list-style-type: none"> <li>Granulomatous diseases, diabetes, vasculitis</li> </ul>	

Hoarseness



Table 3. Differential Diagnosis of Hoarseness

Infectious	<ul style="list-style-type: none"><li>Acute/chronic laryngitis</li><li>Laryngotracheobronchitis (croup)</li></ul>	
Inflammatory	<ul style="list-style-type: none"><li>GERD</li><li>Vocal cord polyps/nodules</li><li>Lifestyle: smoking, chronic EtOH use</li></ul>	
Trauma	<ul style="list-style-type: none"><li>External laryngeal trauma</li><li>Endoscopy and endotracheal tube (e.g. intubation granuloma)</li></ul>	
Neoplasia	<ul style="list-style-type: none"><li>Benign tumour</li><li>Papillomas (HPV infection)</li><li>Minor salivary gland tumours</li><li>Other</li></ul>	<ul style="list-style-type: none"><li>Malignant tumours (i.e. thyroid)</li><li>SCC</li><li>Other</li></ul>
Cysts	<ul style="list-style-type: none"><li>Retention cysts</li></ul>	
Systemic	<ul style="list-style-type: none"><li>Endocrine</li><li>Hypothyroidism</li><li>Virilization</li></ul>	<ul style="list-style-type: none"><li>Connective tissue disease</li><li>RA</li><li>SLE</li></ul>
Neurologic (vocal cord paralysis due to superior ± recurrent laryngeal nerve injury)	<ul style="list-style-type: none"><li>Central lesions<ul style="list-style-type: none"><li>Cerebrovascular accident (CVA)</li><li>Head injury</li><li>Multiple sclerosis (MS)</li><li>Skull base tumours</li><li>Arnold-Chiari malformation</li></ul></li><li>Peripheral lesions<ul style="list-style-type: none"><li>Unilateral</li><li>Lung malignancy</li></ul></li></ul>	<ul style="list-style-type: none"><li>Iatrogenic injury – thyroid, parathyroid surgery, carotid endarterectomy, patent ductus arteriosus (PDA) ligation</li><li>Bilateral<ul style="list-style-type: none"><li>Iatrogenic injury: bilateral thyroid surgery, forceps delivery</li></ul></li><li>Neuromuscular<ul style="list-style-type: none"><li>Myasthenia gravis</li></ul></li></ul>
Functional	<ul style="list-style-type: none"><li>Psychogenic aphonia (hysterical aphonia)</li></ul>	
Congenital	<ul style="list-style-type: none"><li>Laryngomalacia</li><li>Laryngeal web</li><li>Laryngeal atresia</li></ul>	



Lung malignancy is the most common cause of extralaryngeal vocal cord paralysis.

Neck Mass

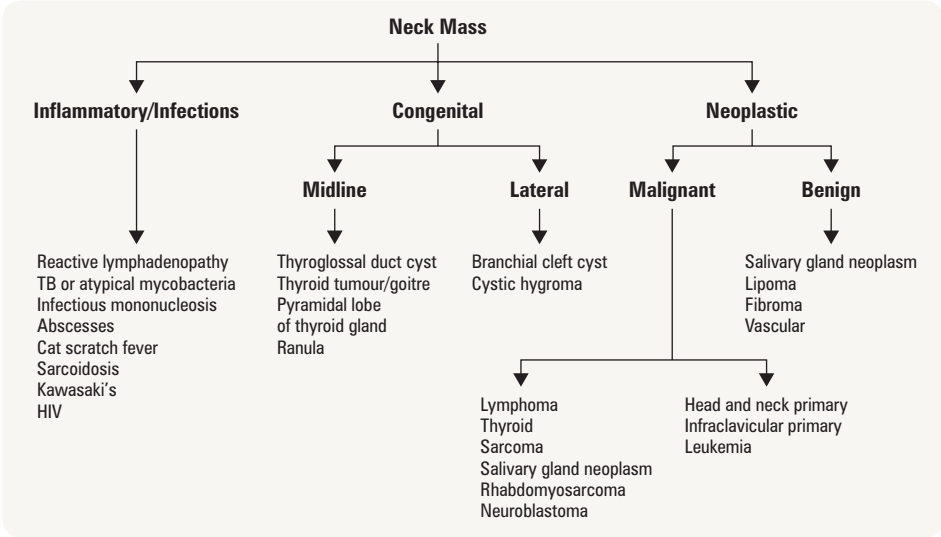


Figure 15. Differential diagnosis of a neck mass

# Hearing

## Normal Hearing Physiology

- **Conductive pathway (external auditory canal to cochlea):** air conduction of sound energy down the EAC → vibration of the tympanic membrane (area effect) → sequential vibration of the middle ear ossicles: malleus, incus, stapes (lever effect) → transmission of amplified vibrations from the stapes footplate in the middle ear to the oval window of the cochlea in the inner ear → pressure differential on cochlear fluid creates movement along the basilar membrane within the cochlea from base to apex
- **Neural pathway (nerve to brain):** basilar membrane vibration stimulates overlying hair cells in the organ of Corti → stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII → cochlear nucleus → superior olivary nucleus → lateral lemniscus → inferior colliculus → Sylvian fissure of temporal lobe



**Order of the Neural Pathway (with corresponding waves on ABR)**

### E COLI

Eighth cranial nerve (I – II)  
Cochlear nucleus (III)  
Superior Olivary nucleus  
Lateral lemniscus (IV – V)  
Inferior colliculus

## Types of Hearing Loss

### 1. Conductive Hearing Loss (CHL)

- the conduction of sound to the cochlea is impaired
- can be caused by external and middle ear disease

### 2. Sensorineural Hearing Loss (SNHL)

- due to a defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
- can be caused by disease of the cochlea, acoustic nerve (CN VIII), brainstem, or cortex

### 3. Mixed Hearing Loss

- both a conductive hearing loss and a sensorineural hearing loss are present

### Auditory Acuity

- whispered-voice test: mask one ear and whisper into the other
- tuning fork tests (see Table 4) (audiogram is of greater utility)
- sensitivity depends on which tuning fork used (256 Hz, 512 Hz, 1024 Hz)
  - Rinne test:
    - ♦ 512 Hz tuning fork is struck and held firmly on mastoid process to test BC. The tuning fork is then placed beside the pinna to test AC
    - ♦ If AC > BC → positive Rinne, which is normal
  - Weber test:
    - ♦ 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative) or is lateralized to one side (Weber right, Weber left)
    - ♦ can place vibrating fork on patient's chin while they clench their teeth, or directly on teeth to elicit more reliable response
    - ♦ will only lateralize if difference in hearing loss between ears is >6 dB



Weber Test Lateralization = ipsilateral conductive hearing loss or contralateral sensorineural hearing loss. When conductive hearing loss is present, the Weber test is more sensitive in detecting the CHL than the Rinne test.



HL = Intensity x Duration



**Table 4. The Interpretation of Tuning Fork Tests**

Examples	Weber	Rinne
Normal or bilateral sensorineural hearing loss	Central	AC > BC (+) bilaterally
Right-sided conductive hearing loss, normal left ear	Lateralizes to right	BC > AC (–) right
Right-sided sensorineural hearing loss, normal left ear	Lateralizes to left	AC > BC (+) bilaterally
Right-sided severe sensorineural hearing loss or dead right ear, normal left ear	Lateralizes to left	BC > AC (–) right*

\* a vibrating tuning fork on the mastoid stimulates the cochlea bilaterally, therefore in this case, the left cochlea is stimulated by the Rinne test on the right, i.e. a false negative test. These tests are not valid if the ear canals are obstructed with cerumen (i.e. will create conductive loss)



Frequency of Tuning Fork (Hz)	Minimum hearing loss to have NEGATIVE Rinne (BC > AC) (dB)
256	15
512	30
1024	45

## Pure Tone Audiometry

- a threshold is the lowest intensity level at which a patient can hear the tone 50% of the time
- thresholds are obtained for each ear for frequencies 250 to 8000 Hz
- air conduction thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function
- bone conduction thresholds are obtained with bone conduction oscillators which bypass the outer and middle ear

### Degree of Hearing Loss

- determined on basis of the pure tone average (PTA) at 500, 1000, and 2000 Hz



**Range of Frequencies Audible to Human Ear:**

- 20 to 20000 Hz
- Most sensitive frequencies: 1000 to 4000 Hz
- Range of human speech: 500 to 2000 Hz

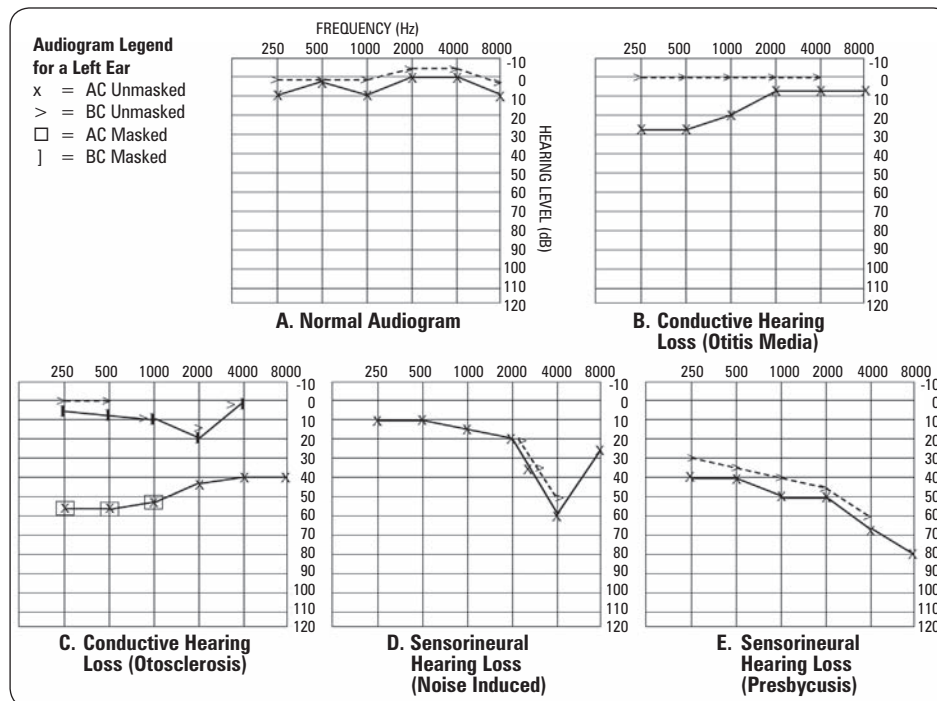


Figure 16. Types of hearing loss and associated audiograms of a left ear

## PURE TONE PATTERNS

### 1. Conductive Hearing Loss (CHL) (Figure 16B and 16C)

- BC in normal range
- AC outside of normal range
- gap between AC and BC thresholds >10 dB (an air-bone gap)

### 2. Sensorineural Hearing Loss (SNHL) (Figure 16D and 16E)

- both air and bone conduction thresholds below normal
- gap between AC and BC <10 dB (no air-bone gap)

### 3. Mixed Hearing Loss

- both air and bone conduction thresholds below normal
- gap between AC and BC thresholds >10 dB (an air-bone gap)



Hearing loss most often occurs at higher frequencies. Noise-induced (occupational) HL is seen at 4000 Hz. HL associated with otosclerosis is seen at 2000 Hz (Carhart's notch).



Air conduction thresholds can only be equal to or greater than bone conduction thresholds.



### Degree of Hearing Loss

Decibel Loss	Degree of Hearing Loss
0 to 20 dB	Normal
21 to 40 dB	Mild
41 to 55 dB	Moderate
56 to 70 dB	Moderate – Severe
71 to 90 dB	Severe
≥91 dB	Profound

## Speech Audiometry

### Speech Reception Threshold (SRT)

- lowest hearing level at which patient is able to repeat 50% of two syllable words which have equal emphasis on each syllable (spondee words)
- SRT and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB. If not, suspect a retrocochlear lesion or functional hearing loss
- used to assess the reliability of the pure tone audiometry

### Speech Discrimination Test

- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at a level 35 to 50 dB > SRT, therefore degree of hearing loss is taken into account
- patients with normal hearing or conductive hearing loss score >90%
- score depends on extent of SNHL
- rollover effect: a decrease in discrimination as sound intensity increases. Typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears as asymmetry may indicate a retrocochlear lesion
- used as best predictor of hearing aid response: if patient has HL and problems with word discrimination, hearing aids may not be helpful



## Impedance Audiometry

### Tympanogram

- the Eustachian tube equalizes the pressure between the external and middle ear
- tympanograms graph the compliance of the middle ear system against a pressure gradient ranging from  $-400$  to  $+200$  mmH<sub>2</sub>O
- tympanogram peak occurs at the point of maximum compliance: where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range:  $-100$  to  $+50$  mmH<sub>2</sub>O

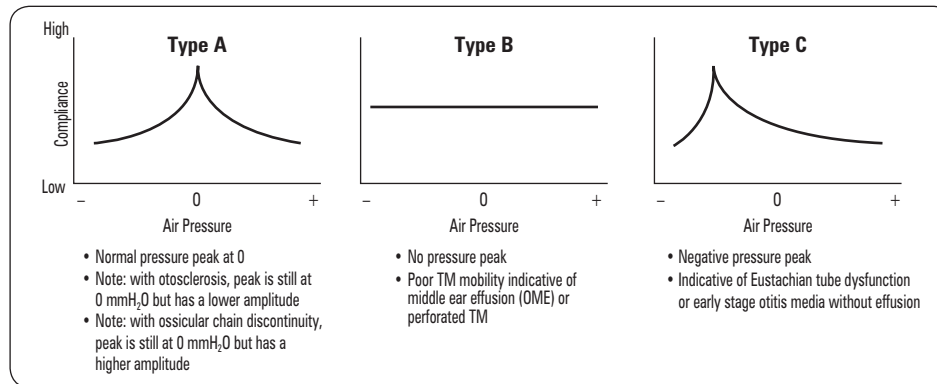


Figure 17. Tympanograms

### Static Compliance

- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0.3 to 1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of greater than 2 cc in children and 2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

### Acoustic Stapedial Reflexes

- stapedius muscle contracts due to loud sound
- acoustic reflex thresholds** = 70 to 100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
- stimulating either ear causes bilateral and symmetrical reflexes
- for reflex to be present, CN VII must be intact and no conductive hearing loss in monitored ear
- if reflex is absent without conductive or severe sensorineural loss, suspect CN VII lesion
- acoustic reflex decay test** = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
- normally, little reflex decay occurs at 500 and 1000 Hz
- with cochlear hearing loss, acoustic reflex thresholds are 25 to 60 dB
- with retrocochlear hearing loss (acoustic neuroma), absent acoustic reflexes or marked reflex decay (>50%) within 5 s

## Auditory Brainstem Response (ABR)

- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (refer to *Order of Neural Pathway* sidebar on OT9). This test can be used to map the lesion according to the site of the defect
- delay in brainstem response suggests cochlear or retrocochlear abnormalities
- does not require volition or co-operation of patient (therefore of value in children and in malingers)

## Otoacoustic Emissions

- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- often used in newborn screening
- can be used to uncover normal hearing in malingering patients
- absence of emissions can be due to hearing loss or fluid in the middle ear

## Aural Rehabilitation

- dependent on degree of hearing loss, communicative requirements, motivation, expectations, age, and physical and mental abilities
- negative prognostic factors:
  - poor speech discrimination
  - narrow dynamic range (recruitment)
  - unrealistic expectations
- types of hearing aids:
  - BTE: behind the ear (with occlusive mould or open fit which allows natural sound to pass – for milder hearing losses)
  - ITE: in-the-ear, placed in concha
  - ITC: in-the-canal, placed entirely in ear canal
  - CIC: contained-in-canal, placed deeply in ear canal
  - bone conduction – bone-anchored hearing aid (BAHA): attached to the skull
  - contralateral routing of signals (CROS)
- assistive listening devices:
  - direct/indirect audio output
  - infrared, FM radio, or induction loop systems
  - telephone, television, or alerting devices
- cochlear implants:
  - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
  - for profound bilateral sensorineural hearing loss not rehabilitated with conventional hearing aids
  - established indication: post-lingually deafened adults, pre- and post-lingually deaf children



**Pre-lingual deafness:** deafness occurring before speech and language are acquired.

**Post-lingual deafness:** deafness occurring after speech and language are acquired.



Pre-lingually deaf infants are the best candidates for aural rehabilitation because they have maximal benefit from ongoing developmental plasticity.



### Bone Anchored Hearing Aids (BAHA)

BAHAs function based on bone conduction and are indicated primarily for patients with conductive hearing loss, unilateral hearing loss, and mixed hearing loss who cannot wear conventional hearing aids. BAHAs consist of a titanium implant, an external abutment, and a sound processor. The sound processor transmits vibrations through the external abutment to the titanium implant and then directly to the cochlea.

## Vertigo

### Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
  - vertigo is produced by peripheral (inner ear) or central (brainstem-cerebellum) stimulation
- it is important to distinguish vertigo from other disease entities that may present with similar complaints of “dizziness” (e.g. cardiovascular, psychiatric, neurological, aging)

**Table 5. Peripheral vs. Central Vertigo**

Symptoms	Peripheral	Central
Imbalance	Moderate-severe	Mild-moderate
Nausea and vomiting	Severe	Variable
Auditory symptoms	Common	Rare
Neurologic symptoms	Rare	Common
Compensation	Rapid	Slow
Nystagmus	Unidirectional Horizontal or rotatory	Bidirectional Horizontal or vertical

**Table 6. Differential Diagnosis of Vertigo Based on History**

Condition	Duration	Hearing Loss	Tinnitus	Aural Fullness	Other Features
Benign paroxysmal positional vertigo (BPPV)	Seconds	–	–	–	
Menière's disease	Minutes to hours Precedes attack	Uni/bilateral, fluctuating	+	Pressure/warmth	
Vestibular neuronitis	Hours to days	–	–	–	
Labyrinthitis	Days	Unilateral	Whistling	–	Recent AOM
Acoustic neuroma	Chronic	Progressive	+	–	Ataxia CN VII palsy

## Benign Paroxysmal Positional Vertigo (BPPV)

### Definition

- acute attacks of transient vertigo lasting **seconds to minutes** initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)

### Etiology

- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
  - can affect each of the 3 semicircular canals, although the posterior canal is affected in >90% of cases



BPPV is the most common cause of episodic vertigo. Patients often are symptomatic when rolling over in bed or moving their head to a position of extreme posterior extension such as looking up at a tall building or getting their hair washed at the hairdresser.

- causes: head injury, viral infection (URTI), degenerative disease, idiopathic
- results in slightly different signals being received by the brain from the two balance organs resulting in sensation of movement

### Diagnosis

- history
- positive Dix-Hallpike maneuver (sensitivity 82%, specificity 71%)

### Dix-Hallpike Positional Testing (see website for video and illustrations)

- the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45° and neck extended 20° holding the position for 20 s
- onset of vertigo and rotary nystagmus indicate a positive test for the dependent side

### Treatment

- reassure patient that process resolves spontaneously
- particle repositioning maneuvers
  - Epley maneuver (performed by MD)
  - Brandt-Daroff exercises (performed by patient)
- surgery for refractory cases
- anti-emetics for nausea/vomiting
- drugs to suppress the vestibular system delay eventual recovery and are therefore not used



Patients can wear Frenzel's magnifying eyeglasses during the Dix-Hallpike maneuver, which inhibit visual fixation and allow for better visualization of the eyes.



### 5 Signs of BPPV Seen with Dix-Hallpike Maneuver

- Geotropic rotatory nystagmus (nystagmus **MUST** be present for a positive test)
- Fatigues with repeated maneuver and fixation
- Reversal of nystagmus upon sitting up
- Latency of ~20 s
- Crescendo/decrecendo vertigo lasting 20 s



### Diagnostic Criteria for Menière's Disease (must have all three):

- Two spontaneous episodes of rotational vertigo ≥20 minutes
- Audiometric confirmation of SNHL (often low frequency)
- Tinnitus and/or aural fullness



**Drop Attacks (Tumarkin's Otolithic Crisis)** are sudden falls occurring without warning and without LOC.



Before proceeding with gentamicin treatment, perform a gadolinium enhanced MRI to rule out CPA tumour as the cause of symptoms.

## Menière's Disease (Endolymphatic Hydrops)

### Definition

- episodic attacks of tinnitus, hearing loss, aural fullness, and vertigo lasting **minutes to hours**

### Proposed Etiology

- inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth

### Epidemiology

- peak incidence 40 to 60 yr
- bilateral in 35% of cases

### Clinical Features

- vertigo, fluctuating low frequency SNHL, tinnitus, and aural fullness
- ± drop attacks (Tumarkin crisis), ± nausea and vomiting
- vertigo disappears with time (minutes to hours), but hearing loss remains
- early in the disease: fluctuating SNHL
- later stages: persistent tinnitus and progressive hearing loss
- attacks come in clusters and can be debilitating to the patient
- triggers: high salt intake, caffeine, stress, nicotine, and alcohol

### Treatment

- acute management may consist of bed rest, antiemetics, antivertiginous drugs [e.g. betahistine (Serc®)], and low molecular weight dextrans (not commonly used)
- long term management may include:
  - medical:
    - ♦ low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
    - ♦ Serc® prophylactically to decrease intensity of attacks
    - ♦ local application of gentamicin to destroy vestibular end-organ, results in complete SNHL
  - surgical:
    - ♦ selective vestibular neurectomy or transtympanic labyrinthectomy
    - ♦ vestibular implants have recently been introduced, experimentally
- must monitor opposite ear as bilaterality occurs in 35% of cases

## Vestibular Neuronitis

### Definition

- acute onset of disabling vertigo often accompanied by nausea, vomiting, and imbalance without hearing loss that resolves over **days** leaving a residual imbalance that lasts **days to weeks**

### Etiology

- thought to be due to a viral infection (e.g. measles, mumps, herpes zoster)
- ~30% of cases have associated URTI symptoms
- other: microvascular events, diabetes, autoimmune process
- considered to be the vestibular equivalent of Bell's palsy, sudden hearing loss, and acute vocal cord palsy

**Clinical Features**

- acute phase:
  - severe vertigo with nausea, vomiting, and imbalance lasting 1 to 5 d
  - irritative nystagmus (fast phase towards the offending ear)
  - patient tends to veer towards affected side
- convalescent phase:
  - imbalance and motion sickness lasting days to weeks
  - spontaneous nystagmus away from affected side
  - gradual vestibular adaptation requires weeks to months
- incomplete recovery likely with the following risk factors: elderly, visual impairment, poor ambulation
- repeated attacks can occur

**Treatment**

- acute phase:
  - bed rest, vestibular sedatives (Gravol®), diazepam
- convalescent phase:
  - progressive ambulation especially in the elderly
  - vestibular exercises: involve eye and head movements, sitting, standing, and walking

## Labyrinthitis

**Definition**

- acute infection of the inner ear resulting in vertigo and hearing loss

**Etiology**

- may be serous (viral) or purulent (bacterial)
- occurs as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures
- bacterial: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *P. aeruginosa*, *P. mirabilis*
- viral: rubella, CMV, measles, mumps, varicella zoster

**Clinical Features**

- sudden onset of vertigo, nausea, vomiting, tinnitus, and unilateral hearing loss, with no associated fever or pain
- meningitis is a serious complication

**Investigations**

- CT head
- if meningitis is suspected: lumbar puncture, blood cultures

**Treatment**

- treat with IV antibiotics, drainage of middle ear ± mastoidectomy

## Acoustic Neuroma (Vestibular Schwannoma)

**Definition**

- schwannoma of the vestibular portion of CN VIII

**Pathogenesis**

- starts in the internal auditory canal and expands into cerebellopontine angle (CPA), compressing cerebellum and brainstem
- when associated with type 2 neurofibromatosis (NF2): bilateral acoustic neuromas, café-au-lait skin lesions, and multiple intracranial lesions

**Clinical Features**

- usually presents with unilateral SNHL or tinnitus
- dizziness and unsteadiness may be present, but true vertigo is rare as tumour growth occurs slowly and thus compensation occurs
- facial nerve palsy and trigeminal (V<sub>1</sub>) sensory deficit (corneal reflex) are late complications

**Diagnosis**

- MRI with gadolinium contrast is the gold standard
- audiogram (to assess SNHL)
- poor speech discrimination relative to the hearing loss
- stapedial reflex absent or significant reflex decay
- ABR – increase in latency of the 5th wave
- vestibular tests: normal or asymmetric caloric weakness (an early sign)

**Treatment**

- expectant management if tumour is very small, or in elderly
- definitive management is surgical excision
- other options: gamma knife, radiation



Acoustic neuroma is the most common intracranial tumour causing SNHL and the most common cerebellopontine angle tumour.



In the elderly, unilateral tinnitus or SNHL is acoustic neuroma until proven otherwise.

# Tinnitus



## Definition

- an auditory perception in the absence of an acoustic stimuli, likely related to loss of input to neurons in central auditory pathways and resulting in abnormal firing

## History

- subjective vs. objective (see Figure 14, OT7)
- continuous vs. pulsatile (vascular in origin)
- unilateral vs. bilateral
- associated symptoms: hearing loss, vertigo, aural fullness, otalgia, otorrhea

## Investigations

- audiology
- if unilateral:
  - ABR, gadolinium enhanced MRI to exclude a retrocochlear lesion
  - CT to diagnose glomus tympanicum (rare)
  - MRI or angiogram to diagnose AVM
- if suspect metabolic abnormality: lipid profile, TSH

## Treatment

- if a cause is found, treat the cause (e.g. drainage of middle ear effusion, embolization or excision of AVM)
- with no treatable cause: 50% will improve, 25% worsen, 25% remain the same
- avoid loud noise, ototoxic meds, caffeine, smoking
- tinnitus clinics
- identify situations where tinnitus is most bothersome (e.g. quiet times), mask tinnitus with soft music or “white noise”
- hearing aid if coexistent hearing loss
- tinnitus instrument: combines hearing aid with white noise masker
- trial of tocainamide

# Diseases of the External Ear

## Cerumen Impaction

### Etiology

- ear wax is a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

### Risk Factors

- hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

### Clinical Features

- hearing loss (conductive)
- ± tinnitus, vertigo, otalgia, aural fullness

### Treatment

- ceruminolytic drops (bicarbonate solution, olive oil, glycerine, Cerumenol®, Cerumenex®)
- syringing
- manual debridement (by MD)



Cerumen impaction is the most common cause of conductive hearing loss for those aged 15-50 yr.



### Syringing

#### Indications:

- Totally occlusive cerumen with pain, decreased hearing, or tinnitus

#### Contraindications:

- Active infection
- Previous ear surgery
- Only hearing ear
- TM perforation

#### Complications:

- Otitis externa
- TM perforation
- Trauma
- Pain
- Vertigo
- Tinnitus
- Otitis media

#### Method:

- Establish that TM is intact
- Gently pull the pinna superiorly and posteriorly
- Using warm water, aim the syringe nozzle upwards and posteriorly to irrigate the ear canal

## Exostoses

### Definition

- bony protuberances in the external auditory canal composed of lamellar bone

### Etiology

- possible association with swimming in cold water

### Clinical Features

- usually an incidental finding
- if large, they can cause cerumen impaction or otitis externa

### Treatment

- no treatment required unless symptomatic

## Otitis Externa (OE)

### Etiology

- bacteria (~90% of OE): *Pseudomonas aeruginosa*, *Pseudomonas vulgaris*, *E. coli*, *S. aureus*
- fungus: *Candida albicans*, *Aspergillus niger*

### Risk Factors

- associated with swimming ("swimmer's ear")
- mechanical cleaning (Q-tips®), skin dermatitis, aggressive scratching
- devices that occlude the ear canal: hearing aids, headphones, etc.

### Clinical Features

- acute:
  - pain aggravated by movement of auricle (traction of pinna or pressure over tragus)
  - otorrhea (sticky yellow purulent discharge)
  - conductive hearing loss ± aural fullness 2° to obstruction of external canal by swelling and purulent debris
  - post-auricular lymphadenopathy
  - complicated OE exists if the pinna and/or the periauricular soft tissues are erythematous and swollen
- chronic:
  - pruritus of external ear ± excoriation of ear canal
  - atrophic and scaly epidermal lining, ± otorrhea, ± hearing loss
  - wide meatus but no pain with movement of auricle
  - tympanic membrane appears normal



Pulling on the pinna is extremely painful in otitis externa, but is usually well tolerated in otitis media.

### Treatment

- clean ear under magnification with irrigation, suction, dry swabbing, and C&S
- bacterial etiology
  - antipseudomonal otic drops (e.g. ciprofloxacin) or a combination of antibiotic and steroid (e.g. Cipro HC®)
  - do not use aminoglycoside if the tympanic membrane (TM) is perforated because of the risk of ototoxicity
  - introduction of fine gauze wick (pope wick) if external canal edematous
  - ± 3% acetic acid solution to acidify ear canal (low pH is bacteriostatic)
  - systemic antibiotics if either cervical lymphadenopathy or cellulitis is present
- fungal etiology
  - repeated debridement and topical antifungals (gentian violet, Mycostatin® powder, boric acid, Locacorten®, Vioform® drops)
- ± analgesics
- chronic otitis externa (pruritus without obvious infection) → corticosteroid alone (e.g. diprosalic acid)

## Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)



### Definition

- osteomyelitis of the temporal bone

### Epidemiology

- occurs in elderly diabetics and immunocompromised patients

### Etiology

- rare complication of otitis externa
- *Pseudomonas* infection in 99% of cases

### Clinical Features

- otalgia and purulent otorrhea that is refractory to medical therapy
- granulation tissue on the floor of the auditory canal

### Complications

- cranial nerve palsies (most commonly VII>X>XI)
- systemic infection, death

### Management

- imaging: high resolution temporal bone CT scan, gadolinium enhanced MRI, technetium scan
- requires hospital admission, debridement, IV antibiotics, hyperbaric O<sub>2</sub>
- may require OR for debridement of necrotic tissue/bone



#### Gallium and Technetium Scans

Gallium scans are used to show sites of active infection. Gallium is taken up by PMNs and therefore only lights up when active infection is present. It will not show the extent of osteomyelitis. Technetium scans provide information about osteoblastic activity and as such are used to demonstrate sites of osteomyelitis. Technetium scans help with diagnosis whereas gallium scans are useful in follow-up.



## Diseases of the Middle Ear



### Acute Otitis Media (AOM) and Otitis Media with Effusion (OME)

- see *Pediatric Otolaryngology*, OT38

### Cholesteatoma

#### Definition

- a cyst composed of keratinizing squamous epithelium occurring in the middle ear, mastoid, and temporal bone
- two types: congenital and acquired

#### Congenital

- presents as a “small white pearl” behind an intact tympanic membrane (anterior and medial to the malleus) or as a conductive hearing loss
- believed to be due to aberrant migration of external canal ectoderm during development
- not associated with otitis media/Eustachian tube dysfunction

#### Acquired (more common)

- generally occurs as a consequence of otitis media and chronic Eustachian tube dysfunction
- frequently associated with retraction pockets in the pars flaccida (1° acquired) and marginal perforations (2° acquired) of the tympanic membrane
- the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

#### Clinical Features

- symptoms:
  - history of otitis media (especially if unilateral), ventilation tubes, ear surgery
  - progressive hearing loss (predominantly conductive although may get sensorineural hearing loss in late stage)
  - otalgia, aural fullness, fever
- signs:
  - retraction pocket in TM, may contain keratin debris
  - TM perforation
  - granulation tissue, polyp visible on otoscopy
  - malodorous, unilateral otorrhea

#### Complications

**Table 7. Complications of Cholesteatoma**

Local	Intracranial
Ossicular erosion: conductive hearing loss	Meningitis
Inner ear erosion: SNHL, dizziness, and/or labyrinthitis	Sigmoid sinus thrombosis
Temporal bone infection: mastoiditis, petrositis	Intracranial abscess (subdural, epidural, cerebellar)
Facial paralysis	

#### Investigations

- audiogram and CT scan

#### Treatment

- there is no conservative therapy for cholesteatoma
- surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction



#### Mechanisms of Cholesteatoma Formation

- Epithelial migration through TM perforation (2° acquired)
- Invagination of TM (1° acquired)
- Metaplasia of middle ear epithelium or basal cell hyperplasia (congenital)

## Mastoiditis

#### Definition

- infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two weeks after onset of untreated or inadequately treated acute suppurative otitis media

#### Etiology

- acute mastoiditis caused by the same organisms as AOM: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, *S. aureus*, *P. aeruginosa*



Complications of AOM are rare due to rapid and effective treatment of AOM with antibiotics.

**Clinical Features**

- otorrhea
- tenderness to pressure over the mastoid
- retroauricular swelling with protruding ear
- fever, hearing loss,  $\pm$  TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)

**Treatment**

- IV antibiotics with myringotomy and ventilation tubes – usually all that is required acutely
- cortical mastoidectomy:
  - debridement of infected tissue allowing aeration and drainage
- indications for surgery:
  - failure of medical treatment after 48 h
  - symptoms of intracranial complications
  - aural discharge persisting for 4 wk and resistant to antibiotics

**Classic Triad**

- Otorrhea
- Tenderness to pressure over the mastoid
- Retroauricular swelling with protruding ear

## Otosclerosis

**Definition**

- fusion of stapes footplate to oval window so that it cannot vibrate

**Etiology**

- autosomal dominant, variable penetrance approximately 40%
- female > male, progresses during pregnancy (hormone responsive)

**Clinical Features**

- progressive conductive hearing loss first noticed in teens and 20s (may progress to sensorineural hearing loss if cochlea involved)
- $\pm$  pulsatile tinnitus
- tympanic membrane normal  $\pm$  pink blush (Schwartz's sign) associated with the neovascularization of otosclerotic bone
- characteristic dip at 2000 Hz (Carhart's notch) on audiogram (see Figure 16C, OT10)



Otosclerosis is the 2<sup>nd</sup> most common cause of conductive hearing loss in 15 to 50 year olds (after cerumen impaction).

**Treatment**

- monitor with serial audiograms if coping with loss
- hearing aid (air conduction, bone conduction, BAHA)
- stapedectomy or stapedotomy (with laser or drill) with prosthesis is definitive treatment

## Diseases of the Inner Ear

### Congenital Sensorineural Hearing Loss

**Hereditary Defects**

- non-syndrome associated (70%):
  - often idiopathic, autosomal recessive
  - connexin 26 (GJB2) most common
- syndrome associated (30%):
  - Waardenburg: white forelock, heterochromia iridis (each eye different color), wide nasal bridge and increased distance between medial canthi
  - Pendred: deafness associated with thyroid gland disorders, SLC26A4 gene, enlarged vestibular aqueducts
  - Treacher-Collins: first and second branchial cleft anomalies
  - Alport: hereditary nephritis

**Prenatal TORCH Infections**

- toxoplasmosis, rubella, CMV, herpes simplex, others (e.g. HIV, syphilis)

**Perinatal**

- Rh incompatibility
- anoxia
- hyperbilirubinemia
- birth trauma (hemorrhage into inner ear)

**Postnatal**

- meningitis, mumps, measles

**High Risk Factors (for Hearing Loss in Newborns)**

- low birth weight/prematurity
- perinatal anoxia (low APGARs)
- kernicterus: bilirubin >25 mg/dL
- craniofacial abnormality
- family history of deafness in childhood
- 1st trimester illness: TORCH infections
- neonatal sepsis
- ototoxic drugs
- perinatal infection, including post-natal meningitis
- consanguinity
- 50-75% of newborns with sensorineural hearing loss have at least one of the above risk factors, and 90% of these have spent time in the NICU
- presence of any risk factor: ABR study performed before leaving NICU and at 3 mo adjusted age
- early rehabilitation improves speech and school performance

**Presbycusis****Definition**

- sensorineural hearing loss associated with aging (starting in 5th and 6th decades)

**Etiology**

- hair cell degeneration
- age related degeneration of basilar membrane, possibly genetic etiology
- cochlear neuron damage
- ischemia of inner ear

**Clinical Features**

- progressive, bilateral hearing loss initially at high frequencies, then middle frequencies
- loss of discrimination of speech especially with background noise present – patients describe people as mumbling
- recruitment phenomenon: inability to tolerate loud sounds
- tinnitus

**Treatment**

- hearing aid if patient has difficulty functioning, hearing loss >30-35 dB, and good speech discrimination
- ± lip reading, auditory training, auditory aids (doorbell and phone lights)



Presbycusis is the most common cause of SNHL.

**Sudden Sensorineural Hearing Loss****Clinical Features**

- presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, aural fullness
- usually idiopathic, rule out other causes:
  - autoimmune causes (e.g. ESR, rheumatoid factor, ANA)
  - MRI to rule out tumour and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)

**Treatment**

- oral corticosteroids within 3 d of onset: prednisone 1 mg/kg/d for 10-14 d

**Prognosis**

- depends on degree of hearing loss
- 70% resolve within 10 to 14 d
- 20% experience partial resolution
- 10% experience permanent hearing loss



Sudden sensorineural hearing loss may easily be confused with ischemic brain events. It is important to keep a high index of suspicion especially with elderly patients presenting with sudden sensorineural hearing loss as well as vertigo.

**Autoimmune Inner Ear Disease****Etiology**

- idiopathic
- may be associated with systemic autoimmune diseases (i.e. rheumatoid arthritis, SLE), vasculitides (i.e. granulomatosis with polyangiitis, polyarteritis nodosa) and allergies

**Epidemiology**

- most common between ages 20-50

**Clinical Features**

- rapidly progressive or fluctuating bilateral SNHL
- $\pm$  tinnitus, aural fullness, vestibular symptoms (i.e. ataxia, disequilibrium, vertigo)

**Investigations**

- autoimmune work-up: CBC, ESR, ANA, rheumatoid factor

**Treatment**

- high-dose corticosteroids: treat early for at least 30 d
- consider cytotoxic medication for steroid non-responders

## Drug Ototoxicity

**Aminoglycosides**

- streptomycin and gentamicin (vestibulotoxic), kanamycin and tobramycin (cochleotoxic)
- toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
- destroys sensory hair cells: outer first, inner second (therefore otoacoustic emissions are lost first)
- high frequency hearing loss develops earliest
- ototoxicity occurs days to weeks post-treatment
- must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
- q24h dosing recommended (with amount determined by creatinine clearance)
- aminoglycoside toxicity displays saturable kinetics therefore once daily dosing presents less risk than divided daily doses
- duration of treatment is the most important predictor of ototoxicity
- treatment: immediately stop aminoglycosides

**Salicylates**

- hearing loss with tinnitus, reversible if discontinued

**Antimalarials (Quinines)**

- hearing loss with tinnitus
- reversible if discontinued but can lead to permanent loss

**Others**

- many antineoplastic agents are ototoxic (weigh risks vs. benefits)
- loop diuretics

## Noise-Induced Sensorineural Hearing Loss

**Pathogenesis**

- 85 to 90 dB over months or years or single sound impulses  $>135$  dB can cause cochlear damage
- bilateral SNHL initially and most prominently at 4000 Hz (resonant frequency of the temporal bone), known as “boilermaker’s notch” on audiogram, extends to higher and lower frequencies with time (see Figure 16D, OT10)
- speech reception not altered until hearing loss  $>30$  dB at speech frequency, therefore considerable damage may occur before patient complains of hearing loss
- difficulty with speech discrimination, especially in situations with competing noise

**Phases of Hearing Loss**

- dependent on: intensity of sound and duration of exposure
- temporary threshold shift:
  - when exposed to loud sound, decreased sensitivity or increased threshold for sound
  - may have associated aural fullness and tinnitus
  - with removal of noise, hearing returns to normal
- permanent threshold shift:
  - hearing does not return to previous state

**Treatment**

- hearing aid
- prevention:
  - ear protectors: muffs, plugs
  - limit exposure to noise with frequent rest periods
  - regular audiologic follow-up

## Temporal Bone Fractures

Table 8. Features of Temporal Bone Fractures (see Figure 18)

	Transverse (1)	Longitudinal (2)
<b>Extension</b>	Into bony labyrinth and internal auditory meatus	Into middle ear
<b>Incidence</b>	10 to 20%	70 to 90%
<b>Etiology</b>	Frontal/occipital trauma	Lateral skull trauma
<b>CN pathology</b>	CN VII palsy (50%)	CN VII palsy (10 to 20%)
<b>Hearing loss</b>	Sensorineural loss due to direct cochlear injury	Conductive hearing loss secondary to ossicular injury
<b>Vestibular symptoms</b>	Sudden onset vestibular symptoms due to direct semicircular canal injury (vertigo, spontaneous nystagmus)	Rare
<b>Other features</b>	Intact external auditory meatus, tympanic membrane $\pm$ hemotympanum Spontaneous nystagmus CSF leak in Eustachian tube to nasopharynx $\pm$ rhinorrhea (risk of meningitis)	Torn tympanic membrane or hemotympanum Bleeding from external auditory canal Step formation in external auditory canal CSF otorrhea Battle's sign = mastoid ecchymoses Raccoon eyes = periorbital ecchymoses

- characterized as longitudinal or transverse relative to the long axis of the petrous temporal bone
- rarely are temporal bone fractures purely transverse or longitudinal, often it is a mixed picture

### Diagnosis

- otoscopy
- do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
- CT head
- audiology, facial nerve tests (for transverse fractures), Schirmer's test (of lacrimation), stapedial reflexes if CN VII palsy
- if suspecting CSF leak: look for halo sign, send fluid for  $\beta$ -2 transferrin

### Treatment

- ABCs
- medical – expectant, prevent otogenic meningitis
- surgical – explore temporal bone, indications:
  - CN VII palsy (immediate and complete)
  - gunshot wound
  - depressed fracture of external auditory meatus
  - early meningitis (mastoidectomy)
  - bleeding intracranially from sinus
  - CSF otorrhea (may resolve spontaneously)

### Complications

- acute otitis media  $\pm$  labyrinthitis  $\pm$  mastoiditis
- meningitis/epidural abscess/brain abscess
- post-traumatic cholesteatoma

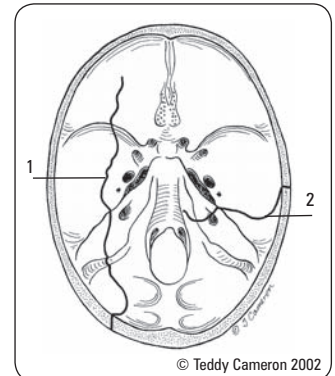


Figure 18. Types of temporal bone fractures



#### Signs of Basilar Skull Fracture

Battle's Sign: ecchymosis of the mastoid process of the temporal bone

Raccoon Eyes

CSF Rhinorrhea/Otorrhea

Cranial Nerve Involvement: facial palsy  
→ CN VII, nystagmus → CN VI, facial numbness → CN V



**The halo sign:** the double ringed appearance of CSF fluid on white filter paper as it separates out from blood.



Hemotympanum can be indicative of temporal bone trauma.



#### House-Brackmann Facial Nerve Grading System

Grade I: Normal facial motor function

Grade II: Mild dysfunction

- Slight weakness
- Normal symmetry and tone at rest
- Complete eye closure

Grade III: Moderate dysfunction

- Obvious weakness
- Grade IV: Moderately severe dysfunction
- Obvious weakness
- $\pm$  disfiguring asymmetry
- Incomplete eye closure
- No forehead motion
- Mouth asymmetric motion

Grade V: Severe dysfunction

- Barely perceptible motion of mouth
- Asymmetric at rest

Grade VI: Total paralysis

- No movement

## Facial Nerve (CN VII) Paralysis

### Etiology

- supranuclear and nuclear (MS, poliomyelitis, cerebral tumours)
- infranuclear (see Table 9)

### Treatment

- treat according to etiology plus provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, gold weighting of upper lid
- facial paralysis that does not resolve with time or with medical treatment will often be referred for possible reanimation techniques to restore function
  - common reanimation techniques include:
    - ♦ direct facial nerve anastomosis
    - ♦ interpositional grafts
    - ♦ anastomosis to other motor nerves
    - ♦ muscle transpositions

Table 9. Differential Diagnosis of Peripheral Facial Paralysis (PFP)

Etiology	Incidence	Findings	Investigations	Treatment, Follow-up, and Prognosis (Px)
<b>Bell's Palsy</b> Idiopathic, (HSV) infection of the facial nerve Diagnosis of exclusion	80 to 90% of PFP  <b>Risk Factors:</b> Diabetes Pregnancy Viral prodrome (50%)	<b>Hx:</b> Acute onset Numbness of ear Schirmer's test Recurrence (12%) + FHx (14%) Hyperacusis (30%)  <b>P/E:</b> Paralysis or paresis of all muscle groups on one side of the face Absence of signs of CNS disease Absence of signs of ear or CPA diseases	Stapedial reflex absent Audiology normal (or baseline) EMG – best measure for prognosis Topographic testing MRI with gadolinium – enhancement of CN VII and VIII High resolution CT	<b>Rx:</b> Protect the eye to prevent exposure keratitis with patching or tarsorrhaphy Systemic steroids may lessen degeneration and hasten recovery Consider antiviral (acyclovir)  <b>F/U:</b> Spontaneous remission should begin within 3 wk of onset Delayed (3 to 6 mo) recovery portends at least some functional loss  <b>Px:</b> 90% recover spontaneously and completely overall; >90% recovery if paralysis was incomplete Poorer if hyperacusis, > 60 yr, diabetes, HTN, severe pain
<b>Ramsay-Hunt Syndrome (Herpes Zoster Oticus)</b> Varicella zoster infection of CN VII/VIII	4.5 to 9% of PFP  <b>Risk Factors:</b> > 60 yr Impaired immunity Cancer Radiotherapy Chemotherapy	<b>Hx:</b> Hyperacusis SNHL Severe pain of pinna, mouth, or face  <b>P/E:</b> Vesicles on pinna, ext. canal (erupt 3-7 d after onset of pain) Associated herpes zoster ophthalmicus (uveitis, keratoconjunctivitis, optic neuritis, or glaucoma)	Stapedial reflex absent Audiology – SNHL Viral ELISA studies to confirm MRI with gadolinium (86% of facial nerves enhance)	<b>Rx:</b> Pt. should avoid touching lesions to prevent spread of infection Systemic steroids can relieve pain, vertigo, avoid postherpetic neuralgia Acyclovir may lessen pain, aid healing of vesicles  <b>F/U:</b> 2 to 4 wk  <b>Px:</b> Poorer prognosis than Bell's palsy; 22% recover completely, 66% incomplete paralysis, 10% complete paralysis
<b>TEMPORAL BONE FRACTURE</b>				
<b>Longitudinal (90%)</b>	20% have PFP	<b>Hx:</b> Blow to side of head  <b>P/E:</b> Trauma to side of head Neuro findings consistent with epidural/subdural bleed	Skull X-rays CT head	<b>Px:</b> Injury usually due to stretch or impingement; may recover with time
<b>Transverse (10%)</b>	40% have PFP	<b>Hx:</b> Blow to frontal or occipital area  <b>P/E:</b> Trauma to front or back of head	Skull X-rays CT head	<b>Px:</b> Nerve transection more likely
<b>Iatrogenic</b>		Variable (depending on level of injury)	Wait for lidocaine to wear off EMG	<b>Rx:</b> Exploration if complete nerve paralysis No exploration if any movement present

Source: Paul Warrick, MD

## Rhinitis

### Definition

- inflammation of the lining (mucosa) of the nasal cavity

Table 10. Classification of Rhinitis

Inflammatory	Non-Inflammatory
<ul style="list-style-type: none"> <li>Perennial non-allergic               <ul style="list-style-type: none"> <li>Asthma, ASA sensitivity</li> </ul> </li> <li>Allergic               <ul style="list-style-type: none"> <li>Seasonal</li> <li>Perennial</li> </ul> </li> <li>Atrophic               <ul style="list-style-type: none"> <li>Primary: <i>Klebsiella ozena</i> (especially in elderly)</li> <li>Acquired: post-surgery if too much mucosa or turbinate has been resected</li> </ul> </li> <li>Infectious               <ul style="list-style-type: none"> <li>Viral: e.g. rhinovirus, influenza, parainfluenza, etc.</li> <li>Bacterial: e.g. <i>S. aureus</i></li> <li>Fungal</li> <li>Granulomatous: TB, syphilis, leprosy</li> </ul> </li> <li>Non-infectious               <ul style="list-style-type: none"> <li>Sarcoidosis</li> <li>Granulomatosis with polyangiitis</li> </ul> </li> <li>Irritant               <ul style="list-style-type: none"> <li>Dust</li> <li>Chemicals</li> <li>Pollution</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Rhinitis medicamentosa               <ul style="list-style-type: none"> <li>Topical decongestants</li> </ul> </li> <li>Hormonal               <ul style="list-style-type: none"> <li>Pregnancy</li> <li>Estrogens</li> <li>Thyroid</li> </ul> </li> <li>Idiopathic vasomotor</li> </ul>



**Rhinitis medicamentosa:** rebound congestion due to the overuse of intranasal vasoconstrictors. For prevention, use of these medications for only 5-7 d is recommended.



**Table 11. Nasal Discharge: Character and Associated Conditions**

Character	Associated Conditions
Watery/mucoid	Allergic, viral, vasomotor, CSF leak (halo sign)
Mucopurulent	Bacterial, foreign body
Serosanguinous	Neoplasia
Bloody	Trauma, neoplasia, bleeding disorder, hypertension/vascular disease

## Allergic Rhinitis (Hay Fever)

### Definition

- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds

### Etiology

- when allergens contact the respiratory mucosa, specific IgE antibody is produced in susceptible hosts
- concentration of allergen in the ambient air correlates directly with the rhinitis symptoms

### Epidemiology

- age at onset usually <20 yr
- more common in those with a personal or family history of allergies/atopy

### Clinical Features

- nasal: obstruction with pruritus, sneezing
- clear rhinorrhea (containing increased eosinophils)
- itching of eyes with tearing
- frontal headache and pressure
- mucosa: swollen, pale, "boggy"
- seasonal (summer, spring, early autumn)
  - pollens from trees
  - lasts several weeks, disappears and recurs following year at same time
- perennial
  - inhaled: house dust, wool, feathers, foods, tobacco, hair, mould
  - ingested: wheat, eggs, milk, nuts
  - occurs intermittently for years with no pattern or may be constantly present

### Complications

- chronic sinusitis/polyps
- serous otitis media

### Diagnosis

- history
- direct exam
- allergy testing

### Treatment

- education: identification and avoidance of allergen
- nasal irrigation with saline
- antihistamines (e.g. diphenhydramine, fexofenadine)
- oral decongestants (e.g. pseudoephedrine, phenylpropanolamine)
- topical decongestant (may lead to rhinitis medicamentosa)
- other topicals: steroids (fluticasone), disodium cromoglycate, antihistamines, ipratropium bromide
- oral steroids if severe
- desensitization by allergen immunotherapy



Congestion reduces nasal airflow and allows the nose to repair itself (i.e. washes away the irritants). Treatment should focus on the initial insult rather than target this defense mechanism.

## Vasomotor Rhinitis

- neurovascular disorder of nasal parasympathetic system (vidian nerve) affecting mucosal blood vessels
- nonspecific reflex hypersensitivity of nasal mucosa
- caused by:
  - temperature change
  - alcohol, dust, smoke
  - stress, anxiety, neurosis
  - endocrine: hypothyroidism, pregnancy, menopause
  - parasympathomimetic drugs
  - beware of rhinitis medicamentosa: reactive vasodilation due to prolonged use (>5 d) of nasal drops and sprays (Dristan®, Otrivin®)

### Clinical Features

- chronic intermittent nasal obstruction, varies from side to side
- rhinorrhea: thin, watery
- mucosa and turbinates: swollen
- nasal allergy must be ruled out

### Treatment

- elimination of irritant factors
- parasympathetic blocker (Atrovent® nasal spray)
- steroids (e.g. beclomethasone, fluticasone)
- surgery (often of limited lasting benefit): electrocautery, cryosurgery, laser treatment or removal of inferior or middle turbinates
- vidian neurectomy (rarely done)
- symptomatic relief with exercise (increased sympathetic tone)

## Rhinosinusitis

### Pathogenesis of Rhinosinusitis

- ostial obstruction or dysfunctional cilia permit stagnant mucous and consequently infection
- all sinuses drain to a common prechamber under the middle meatus called the osteomeatal complex

### Definition

- inflammation of the mucosal lining of the sinuses and nasal passages

### Classification

- acute: <4 wk
- subacute: 4-8 wk
- chronic: >8-12 wk

**Table 12. Etiologies of Rhinosinusitis**

<b>Ostial obstruction</b>	Inflammation	<ul style="list-style-type: none"> <li>• URTI</li> <li>• Allergy</li> </ul>
	Mechanical	<ul style="list-style-type: none"> <li>• Septal deviation</li> <li>• Turbinate hypertrophy</li> <li>• Polyps</li> <li>• Tumours</li> <li>• Adenoid hypertrophy</li> <li>• Foreign body</li> <li>• Congenital abnormalities (e.g. cleft palate)</li> </ul>
	Immune	<ul style="list-style-type: none"> <li>• Granulomatosis with polyangiitis</li> <li>• Lymphoma, leukemia</li> <li>• Immunosuppressed patients (e.g. neutropenics, diabetics, HIV)</li> </ul>
<b>Systemic</b>		<ul style="list-style-type: none"> <li>• Cystic fibrosis</li> <li>• Immotile cilia (e.g. Kartagener's)</li> </ul>
<b>Direct extension</b>	Dental	<ul style="list-style-type: none"> <li>• Infection</li> </ul>
	Trauma	<ul style="list-style-type: none"> <li>• Facial fractures</li> </ul>

## Acute Bacterial Rhinosinusitis

### Definition

- bacterial infection of the paranasal sinuses and nasal passages lasting >7 d
- clinical diagnosis requiring  $\geq 2$  major symptoms, at least one of the symptoms is either nasal obstruction or purulent/dicoloured nasal discharge
  - **major symptoms**
    - ♦ facial pain/pressure/fullness
    - ♦ nasal obstruction
    - ♦ purulent/dicoloured nasal discharge
    - ♦ hyposmia/anosmia
  - **minor symptoms**
    - ♦ headache
    - ♦ halitosis
    - ♦ fatigue
    - ♦ dental pain
    - ♦ cough
    - ♦ ear pain/fullness

### Etiology

- bacteria: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis*, *S. aureus*, anaerobes (dental)
- children are more prone to a bacterial etiology, but viral is still more common
- maxillary sinus most commonly affected
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless, black or pale mucosa on examination)

### Clinical Features

- sudden onset of
  - nasal blockage/congestion and/or purulent nasal discharge/posterior nasal drip
  - $\pm$  facial pain or pressure, hyposmia, sore throat
- persistent/worsening symptoms >5 to 7 d or presence of purulence for 3 to 4 d with high fever
- speculum exam: erythematous mucosa, mucopurulent discharge, pus originating from the middle meatus
- predisposing factors: viral URTI, allergy, dental disease, anatomical defects
- differentiate from acute viral rhinosinusitis (course: <10 d, peaks by 3 d)

### Management

- depends on symptom severity (i.e. intensity/duration of symptoms, impact on quality of life)
- mild-moderate: INCS
  - if no response within 72 h, add antibiotics
- severe: INCS + antibiotics
- antibiotics:
  - 1st line: amoxicillin x 10 d (TMP-SMX or macrolide if penicillin allergy)
- if no response to 1st line antibiotics within 72 h, switch to 2nd line
  - 2nd line: fluoroquinolones or amoxicillin-clavulanic acid inhibitors
- adjuvant therapy (saline irrigation, analgesics, oral/topical decongestant) may provide symptomatic relief
- CT indicated only if complications are suspected



#### Acute Rhinosinusitis Complications

Consider hospitalization if any of the following are suspected

- Orbital (Chandler's classification)
  - Periorbital cellulitis
  - Orbital cellulitis
  - Subperiosteal abscess
  - Orbital abscess
  - Cavernous sinus thrombosis
- Intracranial
  - Meningitis
  - Abscess
- Bony
  - Subperiosteal frontal bone abscess ("Pott's Puffy tumour")
  - Osteomyelitis
- Neurologic
  - Superior orbital fissure syndrome (CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypoesthesia)
  - Orbital apex syndrome (as above, plus neuritis, papilledema, decreased visual acuity)



#### FESS = Functional Endoscopic Sinus Surgery

Opening of the entire osteomeatal complex in order to facilitate drainage while sparing the sinus mucosa.

## Chronic Rhinosinusitis

### Definition

- inflammation of the mucosa of paranasal sinuses and nasal passages >8 to 12 wk
- diagnosis requiring  $\geq 2$  major symptoms for >8 to 12 wk and  $\geq 1$  objective finding of inflammation of the paranasal sinuses (CT/endoscopy)

### Etiology

- unclear etiology but the following may contribute or predispose:
  - inadequate treatment of acute rhinosinusitis
  - bacterial colonization/biofilms
    - ♦ *S. aureus*, *enterobacteriaceae*, *pseudomonas*, *S. pneumoniae*, *H. influenzae*,  $\beta$ -hemolytic *streptococci*
  - fungal infection (e.g. *Aspergillus*, *Zygomycetes*, *Candida*)
  - anatomic abnormality (e.g. lost ostia patency, deviated septum – predisposing factors)
  - allergy/allergic rhinitis
  - ciliary disorder (e.g. cystic fibrosis, Kartagener's)
  - chronic inflammatory disorder (e.g. granulomatosis with polyangiitis)
  - untreated dental disease



Allergic fungal rhinosinusitis is a chronic sinusitis affecting mostly young, immunocompetent, atopic individuals. Treatment options include FESS  $\pm$  intranasal topical steroids, antifungals, and immunotherapy.

**Clinical Features** (similar to acute, but less severe)

- chronic nasal obstruction
- purulent anterior/posterior nasal discharge
- facial congestion/fullness
- facial pain/pressure
- hyposmia/anosmia
- halitosis
- chronic cough
- maxillary dental pain

**Management**

- identify and address contributing or predisposing factors
- obtain CT or perform endoscopy
- if polyps present: INCS, oral steroids  $\pm$  antibiotics (if signs of infection), refer to Otolaryngologist/Head and Neck Surgeon
- if polyps absent: INCS, antibiotics, saline irrigation, oral steroids (severe cases)
- antibiotics for 3 to 6 wk
  - amoxillin-clavulanic acid inhibitors, fluoroquinolone (moxifloxacin), macrolide (clarithromycin), clindamycin, Flagyl® (metronidazole)
- surgery if medical therapy fails or fungal sinusitis: FESS, balloon sinuplasty

**Complications**

- same as acute sinusitis, mucocele

## Epistaxis

**Blood Supply to the Nasal Septum** (see Figure 4, OT3)

1. Superior posterior septum:
    - internal carotid  $\rightarrow$  ophthalmic  $\rightarrow$  anterior/posterior ethmoidal
  2. Posterior septum:
    - external carotid  $\rightarrow$  internal maxillary  $\rightarrow$  sphenopalatine artery  $\rightarrow$  nasopalatine
  3. Lower anterior septum:
    - external carotid  $\rightarrow$  facial artery  $\rightarrow$  superior labial artery  $\rightarrow$  nasal branch
    - external carotid  $\rightarrow$  internal maxillary  $\rightarrow$  descending palatine  $\rightarrow$  greater palatine
- these arteries all anastomose to form Kiesselbach's plexus, located at Little's area (anterior-inferior portion of the cartilaginous septum)
  - bleeding from above middle turbinate is internal carotid, and from below is external carotid



90% of nose bleeds occur in Little's area.

**Table 13. Etiology of Epistaxis**

Type	Causes
<b>Local</b>	Trauma (most common) <ul style="list-style-type: none"> <li>• Fractures: facial, nasal</li> <li>• Self-induced: digital, foreign body</li> </ul>
	Iatrogenic: nasal, sinus, orbit surgery
	Barometric changes
	Nasal dryness: dry air $\pm$ septal deformities
	Septal perforation
<b>Systemic</b>	Chemical: cocaine, nasal sprays, ammonia, etc.
	Coagulopathies <ul style="list-style-type: none"> <li>• Meds: anticoagulants, NSAIDs</li> <li>• Hemophilias, von Willebrand's</li> <li>• Hematological malignancies</li> <li>• Liver failure, uremia</li> </ul>
	Vascular: hypertension, atherosclerosis, Osler-Weber-Rendu (hereditary hemorrhagic telangiectasia)
	Others: GPA, SLE
	Tumours <ul style="list-style-type: none"> <li>• Benign: polyps, inverting papilloma, angiofibroma</li> <li>• Malignant: squamous cell carcinoma, esthesioneuroblastoma</li> </ul>
	Inflammation <ul style="list-style-type: none"> <li>• Rhinitis: allergic, non-allergic</li> <li>• Infections: bacterial, viral, fungal</li> </ul>
	Idiopathic

**Special Cases**

- Adolescent male with unilateral recurrent epistaxis – consider juvenile nasopharyngeal angiofibroma (JNA). This is the most common benign tumour of the nasopharynx
- Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack

**Investigations**

- CBC, PT/PTT (if indicated)
- x-ray, CT as needed

**Treatment**

- locate bleeding and achieve hemostasis

**1. ABCs**

- patient leans forward to minimize swallowing blood and avoid airway obstruction
- apply constant firm pressure for 20 min on cartilaginous part of nose (not bony pyramid)
- if significant bleeding, assess vitals for signs of hemorrhagic shock  $\pm$  IV NS, cross match blood

## 2. Determine Site of Bleeding

- anterior/posterior hemorrhage defined by location in relationship to bony septum
- visualize nasal cavity with speculum
- use cotton pledget with topical lidocaine ± topical decongestant (i.e. Otrivin®) to help identify area of bleeding (often anterior septum)
- if suspicion of bleeding disorder, coagulation workup (platelet number and platelet function assay)

## 3. Control the Bleeding

- first line topical vasoconstrictors (Otrivin®)
- if first line fails and bleeding adequately visualized, cauterize with silver nitrate
- **do not cauterize both sides of the septum** at one time due to risk of septal perforation from loss of septal blood supply

### A. Anterior hemorrhage treatment

- if fail to achieve hemostasis with cauterization:
  - ♦ place anterior pack\* with half inch Vaseline®-soaked ribbon gauze strips layered from nasal floor toward nasal roof extending to posterior choanae or lubricated absorbable packing (i.e. Gelfoam wrapped in Surgicel®) for 2 to 3 d
  - ♦ can also attempt packing with Merocel® or nasal tampons of different shapes
  - ♦ can also apply Floseal® (hemostatic matrix consisting of topical human thrombin and cross-linked gelatin) if other methods fail

### B. Posterior hemorrhage treatment

- if unable to visualize bleeding source, then usually posterior source:
  - ♦ place posterior pack\* using a Foley catheter, gauze pack, or Epistat® balloon
  - ♦ subsequently, layer anterior packing bilaterally
  - ♦ admit to hospital with packs in for 3 to 5 d
  - ♦ watch for complications: hypoxemia (naso-pulmonic reflex), toxic shock syndrome (Rx: remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration

### C. If anterior/posterior packs fail to control epistaxis

- ligation or embolization of culprit arterial supply by interventional radiology
- ± septoplasty

\* antibiotics for any posterior pack or any pack left for >48 h because of risk of toxic shock syndrome

## 4. Prevention

- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of hypertension and coagulopathies

# Hoarseness

## Definitions

- hoarseness: change in voice quality, ranging from voice harshness to voice weakness. Reflects abnormalities anywhere along the vocal tract from oral cavity to lungs
- dysphonia: a general alteration in voice quality
- aphonia: no sound emanates from vocal folds



If hoarseness present for >2 wk in a smoker, laryngoscopy must be done to rule out malignancy.

# Acute Laryngitis

## Definition

- <2 wk inflammatory changes in laryngeal mucosa

## Etiology

- viral: influenza, adenovirus
- bacterial: Group A *Streptococcus*
- mechanical acute voice strain → submucosal hemorrhage → vocal cord edema → hoarseness
- environmental: toxic fume inhalation

## Clinical Features

- URTI symptoms, hoarseness, aphonia, cough attacks, ± dyspnea
- true vocal cords erythematous/edematous with vascular injection and normal mobility

## Treatment

- usually self-limited, resolves within ~1 wk
- voice rest
- humidification
- hydration
- avoid irritants (e.g. smoking)
- treat with antibiotics if there is evidence of coexistent bacterial pharyngitis



## Vocal Cord Paralysis

**Unilateral:** affected cord lies in the paramedian position, inadequate glottic closure during phonation → weak, breathy voice. Usually medializes with time whereby phonation and aspiration improve. Treatment options include voice therapy, injection laryngoplasty (Radiesse), medialization using silastic block.

**Bilateral:** cords rest in midline therefore voice remains good but respiratory function is compromised and may present as stridor. If no respiratory issues, may monitor closely and wait for improvement. If respiratory issues, intubate and will likely require a tracheotomy.

## Chronic Laryngitis

### Definition

- >2 wk inflammatory changes in laryngeal mucosa

### Etiology

- repeated attacks of acute laryngitis
- chronic irritants (dust, smoke, chemical fumes)
- chronic voice strain
- chronic rhinosinusitis with postnasal drip
- chronic alcohol use
- esophageal disorders: GERD, Zenker's diverticulum, hiatus hernia
- systemic: allergy, hypothyroidism, Addison's disease

### Clinical Features

- chronic dysphonia: rule out malignancy
- cough, globus sensation, frequent throat clearing 2° to GERD
- laryngoscopy: cords erythematous, thickened with ulceration/granuloma formation, and normal mobility

### Treatment

- remove offending irritants
- treat related disorders (e.g. antisecretory therapy for GERD)
- speech therapy with voice rest
- ± antibiotics ± steroids to decrease inflammation
- laryngoscopy to rule out malignancy

## Vocal Cord Polyps

### Definition

- structural manifestation of vocal cord irritation
- acutely, polyp forms 2° to capillary damage in the subepithelial space during extreme voice exertion

### Etiology

- most common benign tumour of vocal cords
- voice strain (muscle tension dysphonia)
- laryngeal irritants (GERD, allergies, tobacco)

### Epidemiology

- 30 to 50 yr of age
- M>F

### Clinical Features

- hoarseness, aphonia, cough attacks ± dyspnea
- pedicled or sessile polyp on free edge of vocal cord
- typically polyp asymmetrical, soft, and smooth
- more common on the anterior 1/3 of the vocal cord
- intermittent respiratory distress with large polyps

### Treatment

- avoid irritants
- endoscopic laryngeal microsurgical removal if persistent or if high risk of malignancy



#### Vocal Cords: Polyps vs. Nodules

Polyps	Nodule
Unilateral, asymmetric	Bilateral
Acute onset May resolve spontaneously	Gradual onset Often follow a chronic course
Subepithelial capillary breakage	Acute: submucosal hemorrhage or edema Chronic: hyalinization within submucous lesion
Soft, smooth, fusiform, pedunculated mass	Acute: small, discrete nodules Chronic: hard, white, thickened fibrosed nodules
Surgical excision if persistent or in presence of risk factors for laryngeal cancer	Surgical excision if refractory

## Vocal Cord Nodules

### Definition

- vocal cord callus
- aka "screamer's or singer's nodules"

### Etiology

- early nodules occur 2° to submucosal hemorrhage
- mature nodules result from hyalinization which occurs with long term voice abuse
- chronic voice strain
- frequent URTI, smoke, alcohol



**Epidemiology**

- frequently in singers, children, bartenders, and school teachers
- F>M

**Clinical Features**

- hoarseness worst at end of day
- on laryngoscopy:
  - often bilateral
  - at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords – point of maximal cord vibration
- chronic nodules may become fibrotic, hard, and white

**Treatment**

- voice rest
- hydration
- speech therapy
- avoid irritants
- surgery rarely indicated for refractory nodules

## Benign Laryngeal Papillomas

**Etiology**

- HPV types 6, 11
- possible hormonal influence, possibly acquired during delivery

**Epidemiology**

- biphasic distribution: 1) birth to puberty (most common laryngeal tumour) and 2) adulthood

**Clinical Features**

- hoarseness and airway obstruction
- can seed into tracheobronchial tree
- highly resistant to complete removal
- some juvenile papillomas resolve spontaneously at puberty
- may undergo malignant transformation
- laryngoscopy shows wart-like lesions in supraglottic larynx and trachea

**Treatment**

- microdebridement or CO<sub>2</sub> laser
- adjuvants under investigation: interferon, cidofovir, acyclovir
- HPV vaccine may prevent/decrease the incidence but more research is needed

## Laryngeal Carcinoma

- see *Neoplasms of the Head and Neck*, OT34

## Salivary Glands



### Sialadenitis

**Definition**

- inflammation of salivary glands

**Etiology**

- viral most common (mumps)
- bacterial causes: *S. aureus*, *S. pneumoniae*, *H. influenzae*
- obstructive vs. non-obstructive
- obstructive infection involves salivary stasis and bacterial retrograde flow

**Predisposing Factors**

- HIV
- anorexia/bulimia
- Sjögren's syndrome
- Cushing's, hypothyroidism, DM
- hepatic/renal failure
- meds that increase stasis: diuretics, TCAs,  $\beta$ -blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)

**Clinical Features**

- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- $\pm$  fever
- $\pm$  leukocytosis
- $\pm$  suppurative drainage from punctum of the gland

**Investigations**

- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

**Treatment**

- bacterial: treat with cloxacillin  $\pm$  abscess drainage, sialogogues
- viral: no treatment



Mumps usually presents with bilateral parotid enlargement  $\pm$  sensorineural hearing loss  $\pm$  orchitis.

## Sialolithiasis

**Definition**

- ductal stone (mainly hydroxyapatite) in adults, sand/sludge in children, leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

**Risk Factors**

- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, diabetes, EtOH, hypercalcemia, psychiatric medication)

**Clinical Features**

- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculus

**Investigations**

- ultrasound  $\pm$  sialogram

**Treatment**

- may resolve spontaneously
- encourage salivation to clear calculus
- massage, analgesia, antibiotics, sialogogues (e.g. lemon wedges, sour lemon candies), warm compresses
- remove calculi endoscopically, by dilating duct or orifice, or by excision through floor of the mouth
- if calculus is within the gland parenchyma, the whole gland must be excised



Bilateral enlargement of the parotid glands may be a manifestation of a systemic disease, such as Sjögren's or an eating disorder (i.e. anorexia, bulimia).

## Salivary Gland Neoplasms

**Etiology**

- anatomic distribution
  - parotid gland: 70-85%
  - submandibular gland: 8-15%
  - sublingual gland: 1%
  - minor salivary glands, most concentrated in hard palate: 5-8%
- malignant (see Table 15, OT35 and Table 16, OT36)
- benign
  - benign mixed (pleomorphic adenoma): 80%
  - Warthin's tumour (5 to 10% bilateral, M>F): 10%
  - cysts, lymph nodes and adenomas: 10%
  - oncocytoma: <1%

**Epidemiology**

- 3 to 6% of all head and neck neoplasms in adults
- mean age at presentation: 55 to 65
- M=F



A mass sitting above an imaginary line drawn between the mastoid process and angle of the mandible is a parotid neoplasm until proven otherwise.

## Parotid Gland Neoplasms

### Clinical Features

- 80% benign (pleomorphic adenoma – most common), 20% malignant (mucoepidermoid – most common)
- painless slow-growing mass
- if bilateral, suggests benign process (Warthin's tumour, Sjögren's, bulimia, mumps) or possible lymphoma

### Investigations

- FNA biopsy
- CT or MRI to determine extent of tumour

### Treatment

- treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
- pleomorphic adenomas are excised due to risk of malignant transformation (5% risk over prolonged period of time)
- superficial tumour
  - superficial parotidectomy above plane of CN VII ± radiation
  - incisional biopsy contraindicated
- deep lesion
  - near-total parotidectomy sparing as much of CN VII as possible
  - if CN VII involved then it is removed and cable grafted
- complications of parotid surgery
  - hematoma, infection, salivary fistula, temporary facial paresis, Frey's syndrome (gustatory sweating)

### Prognosis

- benign: excellent, <5% of pleomorphic adenomas may recur
- malignant: dependent on stage and type of malignancy (see OT36)



#### DDx Parotid Tumour

##### Benign

- Pleomorphic adenoma
- Warthin's tumour (more common in men)
- Benign lymphoepithelial cysts

##### Malignant

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma



Frey's syndrome is a post-operative complication characterized by gustatory sweating. It is due to aberrant innervation of cutaneous sweat glands by parasympathetic nerve fibres that are divided during surgery.



## Neck Masses

### Approach to a Neck Mass

- ensure that the neck mass is not a normal neck structure (hyoid, transverse process of C1 vertebra, prominent carotid bulb)
- any neck mass persisting for more than 2 wk should be investigated for possible neoplastic causes

**Table 14. Acquired Causes of Neck Lumps According to Age**

Age (yr)	Possible Causes of Neck Lump		
<20	1. Congenital	2. Inflammatory/Infectious	3. Neoplastic
20-40	1. Inflammatory	2. Congenital	3. Neoplastic
>40	1. Neoplastic	2. Inflammatory	3. Congenital

### Differential Diagnosis

- congenital
  - lateral (branchial cleft cyst, lymphatic/venous/venolymphatic malformation)
  - midline (thyroglossal duct cyst, dermoid cyst, laryngocele)
- infectious/inflammatory
  - reactive lymphadenopathy (2° to tonsillitis, pharyngitis)
  - infectious mononucleosis
  - Kawasaki, Kikuchi, Kimura
  - HIV
  - salivary gland calculi, sialadenitis
  - thyroiditis
- granulomatous disease
  - mycobacterial infections
  - sarcoidosis
- neoplastic
  - lymphoma
  - salivary gland tumours
  - thyroid tumours
  - metastatic malignancy ("unknown primary")



#### Inflammatory vs. Neoplastic Neck Masses

	Inflammatory	Neoplastic
<b>History</b>		
Painful	Y	N
H&N infection	Y	N
Fever	Y	N
Weight loss	N	Y
CA risk factors	N	Y
Age	Younger	Older
<b>Physical</b>		
Tender	Y	N
Rubbery	Y	Occ.
Rock hard	N	Y
Mobile	Y	± fixed

## Evaluation

### Investigations

- history and physical (including nasopharynx and larynx)
- all other investigations and imaging are dependent upon clinical suspicion following history and physical
- laboratory investigations
  - WBC: infection vs. lymphoma
  - Mantoux TB test
  - thyroid function tests and scan
- imaging
  - neck U/S
  - CT scan
  - angiography: vascularity and blood supply to mass
  - radiologic exam of stomach, bowel and sinuses
- biopsy: for histologic examination
  - FNA: least invasive
  - needle biopsy
  - open biopsy: for lymphoma
- identification of possible primary tumour (rule out a metastatic lymph node from an “unknown primary”)
  - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
  - biopsy of normal tissue of nasopharynx, tonsils, base of tongue, and hypopharynx
  - primary identified 95% of time → stage and treat
  - primary occult 5% of time: excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (squamous cell carcinoma)

## Congenital Neck Masses

### Branchial Cleft Cysts/Fistula

#### Embryology

- at the 6th week of development, the 2nd branchial arch grows over the 3rd and 4th arches and fuses with the neighbouring caudal pre-cardial swelling forming the cervical sinus
- 3 types of malformations:
  1. branchial fistula: persistent communication between skin and GI tract
  2. branchial sinus: blind-ended tract opening to skin
  3. branchial cyst: persistent cervical sinus with no external opening

#### Clinical Features

- 2nd branchial cleft malformations most common
  - sinuses and fistulae present in infancy as a small opening anterior to the sternocleidomastoid muscle
  - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following an URTI
- 1st branchial cleft malformations present as sinus/fistula or cyst in preauricular area or over angle of mandible
- 3rd branchial cleft malformations present as recurrent thyroiditis or thyroid abscess and have a tract leading usually to the left pyriform sinus
- there is controversy whether or not 4th branchial cleft anomalies exist, as they may be remnants of the thyrothymic axis

#### Treatment

- surgical removal of cyst or fistula tract
- if infected: allow infection to settle before removal

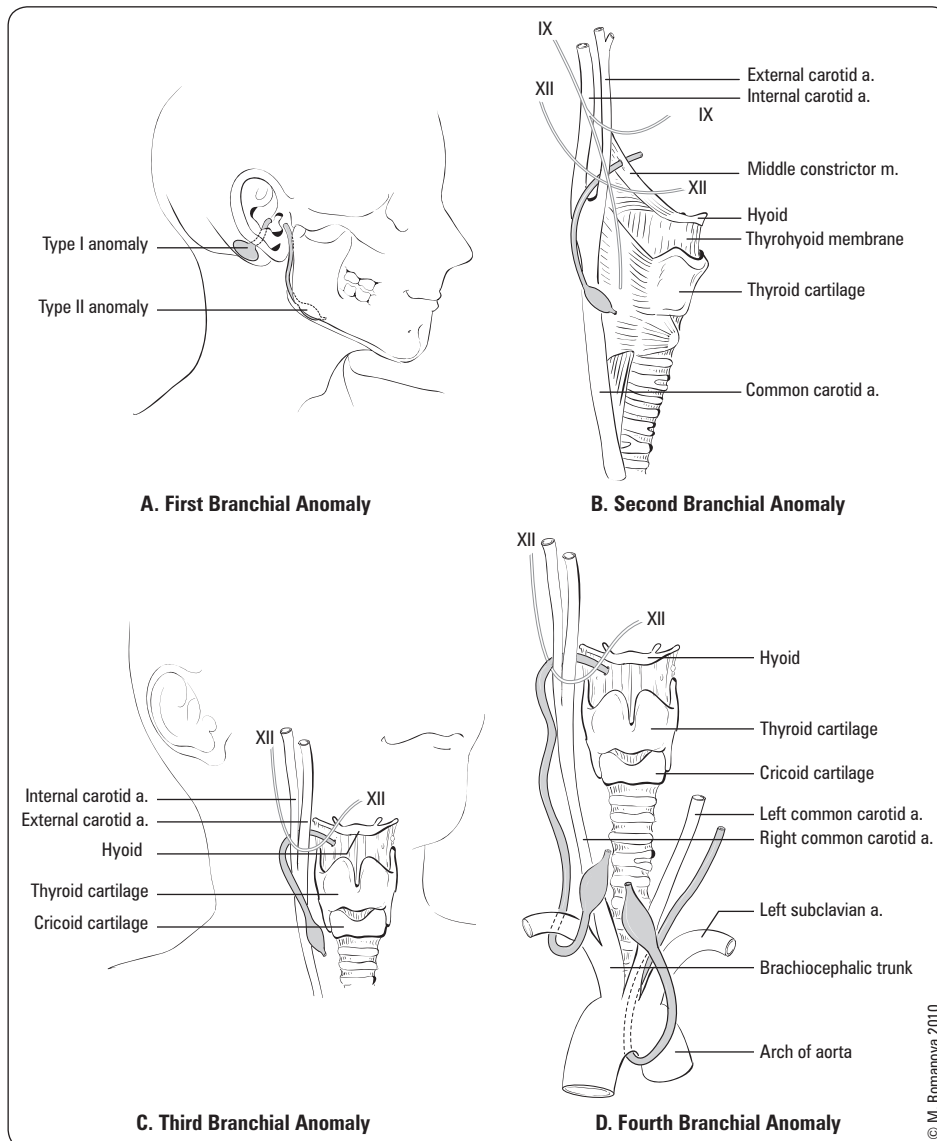


Figure 19. Branchial cleft cysts

## Thyroglossal Duct Cysts

### Embryology

- thyroid originates as ventral midline diverticulum at base of tongue caudal to junction of 3rd and 4th branchial arches (foramen cecum) and migrates down to inferior aspect of neck
- thyroglossal duct cysts are vestigial remnants of tract

### Clinical Features

- usually presents in childhood or 2nd to 4th decades as a midline cyst that enlarges with URTI and elevates with swallowing and tongue protrusion

### Treatment

- pre-operative antibiotics to reduce inflammation
- small potential for neoplastic transformation so complete excision of cyst and tissue around tract up to foramen cecum at base of tongue with removal of central portion of hyoid bone (Sistrunk procedure) recommended

## Lymphatic Malformation

### Definition

- lymphatic malformation arising from vestigial lymph channels of neck

### Clinical Features

- usually present by age 2
- can be macrocystic (composed of large thin-walled cysts, usually below level of mylohyoid muscle) or microcystic (composed of minute cysts, usually above level of mylohyoid muscle)
- usually painless, soft, compressible
- infection causes a sudden increase in size

### Treatment

- can regress spontaneously after bacterial infection, therefore do not plan surgical intervention until several months after infection
- macrocystic lesions can be treated by sclerotherapy or surgical excision
- microcystic lesions are difficult to treat, but can be debulked

## Neoplasms of the Head and Neck

### Pre-Malignant Disease

- leukoplakia
  - hyperkeratosis
  - risk of malignant transformation 5 to 20%
- erythroplakia
  - red superficial patches adjacent to normal mucosa
  - commonly associated with epithelial dysplasia
  - associated with carcinoma in situ or invasive tumour in 40% of cases
- dysplasia
  - histopathologic presence of mitoses and prominent nucleoli
  - involvement of entire mucosal thickness = carcinoma in situ
  - associated progression to invasive cancer in 15 to 30% of cases

### Investigations

- initial metastatic screen includes chest x-ray
- scans of liver, brain, and bone only if clinically indicated
- CT scan is superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI is superior to discriminate tumour from mucus and to detect bone marrow invasion
- ± PET scans

### Treatment

- treatment depends on:
  - histologic grade of tumour
  - stage
  - physical and psychological health of patient
  - facilities available
  - expertise and experience of the medical and surgical oncology team
- in general:
  - 1° surgery for malignant oral cavity tumours with radiotherapy reserved for salvage or poor prognostic indicators
  - 1° radiotherapy for nasopharynx, oropharynx, hypopharynx, larynx malignancies with surgery reserved for salvage
  - palliative chemotherapy for metastatic or incurable disease
  - concomitant chemotherapy increases survival in advanced disease
  - chemotherapy has a role as induction therapy prior to surgery and radiation
  - panendoscopy to detect primary disease when lymph node metastasis is identified
  - anti-EGFR treatment (cetuximab, panitumumab) has a role as concurrent therapy with radiation (for advanced local and regional disease)

### Prognosis

- synchronous tumours occur in 9 to 15% of patients
- late development of 2nd primary most common cause of post-treatment failure after 36 mo



**All patients presenting with a head and neck mass should be asked if they are experiencing the following obstructive, referred, or local symptoms:**

- Dyspnea or stridor (positional vs. non-positional)
- Hoarseness or dysphonia
- Otalgia
- Non-healing oral ulcer
- Dysphagia
- Hemoptysis, hematemesis



**Detection of cervical lymph nodes on physical examination:**  
False negative rate: 15 to 30%  
False positive rate: 30 to 40%



**Pathological lymphadenopathy defined radiographically as:**

- A jugulodigastric node > 1.5 cm in diameter, or a retropharyngeal node > 1 cm in diameter
- A node of any size which contains central necrosis



**Common sites of distant metastases for head and neck neoplasms:**  
lungs > liver > bones



**Table 15. Quick Look-Up Summary of Head and Neck Malignancies – Etiology and Epidemiology**

Etiology	Epidemiology	Risk Factors
<b>Oral Cavity</b>		
95% SCC others: sarcoma, melanoma, minor salivary gland tumour	Mean age: 50 to 60 M>F Most common site of H&N cancers 50% on anterior 2/3 of tongue	Smoking/EtOH Poor oral hygiene Leukoplakia, erythroplakia Lichen planus, chronic inflammation Sun exposure – lip HPV infection
<b>Nose and Paranasal Sinus</b>		
75 to 80% SCC Adenocarcinoma (2 <sup>nd</sup> most common) and mucoepidermoid 99% in maxillary/ethmoid sinus 10% arise from minor salivary glands	Mean age: 50 to 70 Rare tumours ↓ incidence in last 5 to 10 yr	Wood/shoe/textile industry Hardwood dust (nasal/ethmoid sinus) Nickel, chromium (maxillary sinus) Air pollution Chronic rhinosinusitis
<b>Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx and Larynx)</b>		
<b>Nasopharynx</b>		
90% SCC ~10% lymphoma	Mean age: 50 to 59 M:F = 2.4:1 Incidence 0.8 per 100,000 100x increased incidence in Southern Chinese	Epstein-Barr virus (EBV) Salted fish Nickel exposure Poor oral hygiene Genetic – Southern Chinese
<b>Oropharynx</b>		
95% SCC – poorly differentiated	Mean age: 50 to 70 M:F = 4:1	Smoking/EtOH HPV Infection
<b>Hypopharynx</b>		
95% SCC 3 sites: 1. pyriform sinus (60%) 2. post-cricoid (30%) 3. post pharyngeal wall (10%)	Mean age: 50 to 70 M>F 8 to 10% of all H&N cancer	Smoking/EtOH
<b>Larynx</b>		
SCC most common 3 sites: 1. supraglottic (30 to 35%) 2. glottic (60 to 65%) 3. subglottic (1%)	Mean age: 45 to 75 M:F = 10:1 45% of all H&N cancer	Smoking/EtOH HPV 16 infection strongly associated with the risk of laryngeal squamous cell cancers (Li et al., 2013)
<b>Salivary Gland</b>		
40% mucoepidermoid 30% adenoid cystic 5% acinic cell 5% malignant mixed 5% lymphoma	Mean age: 55 to 65 M=F 3 to 6% of all H&N cancer Rate of malignancy: Parotid 15 to 25% Submandibular 37 to 43% Minor salivary >80%	
<b>Thyroid ( 90% benign – 10% malignant)</b>		
>80% papillary 5-15% follicular 5% medullary <5% anaplastic 1 to 5% Hurthle cell 1 to 2% metastatic	Children Adults <30 or >60 Nodules more common in females Malignancy more common in males	Radiation exposure Family history – papillary CA or multiple endocrine neoplasia – MEN II Older age Male Papillary – Gardner's, Cowden's, familial adenomatous polyposis (FAP)
<b>Parathyroid</b>		
	Mean age: 44 to 55 yr Rare tumour	


**Risk Factors for Head and Neck Cancer include:**

- Smoking
- EtOH (this is synergistic with smoking)
- Radiation
- Occupational/Environmental exposures
- Oral HPV infection (independent of smoking and EtOH exposure)



The smaller the salivary gland, the greater the likelihood that a mass in the gland is malignant.

**Table 16. Quick Look-Up Summary of Head and Neck Malignancies – Diagnosis and Treatment**

Clinical Features	Investigations	Treatment	Prognosis
<b>Oral Cavity</b> Asymptomatic neck mass (30%) Non-healing ulcer ± bleeding Dysphagia, sialorrhea, dysphonia Oral fetor, otalgia, leukoplakia or erythroplakia (pre-malignant changes or CIS)	Biopsy CT	1° surgery local resection ± neck dissection ± reconstruction 2° radiation	5 yr survival: - T1/T2: 75% - T3/T4: 30 to 35% Poor prognostic indicators: Depth of invasion, close surgical margins location (tongue worse than floor of mouth) Cervical nodes, extra capsular spread
<b>Nose and Paranasal Sinus</b> <b>Early symptoms:</b> Unilateral nasal obstruction Epistaxis, rhinorrhea <b>Late symptoms:</b> 2° to invasion of nose, orbit, nerves, oral cavity, skin, skull base, cribriform plate	CT/MRI Biopsy	Surgery and radiation Chemoradiotherapy	5 yr survival: 30 to 60% Poor prognosis 2° to late presentation
<b>Nasopharynx</b> Cervical nodes (60 to 90%) Nasal obstruction, epistaxis Unilateral otitis media ± hearing loss CN III to VI, IX to XII (25%) Proptosis, voice change, dysphagia	Nasopharyngoscopy Biopsy CT/MRI	1° radiation, chemoradiation Surgery for limited or recurrent disease	5 yr survival: - I: 79% - II: 72% - III: 50 to 60% - IV: 36 to 42%
<b>Oropharynx</b> Odynophagia, otalgia Ulcerated/enlarged tonsil Fixed tongue/trismus/dysarthria Oral fetor, bloody sputum Cervical lymphadenopathy (60%) Distant mets: lung/bone/liver (7%)	Biopsy CT	1° radiation 2° surgery local resection ± neck dissection ± reconstruction	Base of tongue – control rates T1: >90%, T4: 13 to 52% Tonsils – cure rate T1/T2: 90 to 100%, T4: 15 to 33% HPV-positive tumours have an approximately 20% improved overall survival rate
<b>Hypopharynx</b> Dysphagia, odynophagia Otagia, hoarseness Cervical lymphadenopathy	Pharyngoscopy Biopsy CT	1° radiation 2° surgery	5 yr survival: T1: 53% T2/T3: 36-39% T4: 24%
<b>Larynx</b> Dysphagia, odynophagia, globus Otagia, hoarseness, Dyspnea/stridor Cough/hemoptysis Cervical nodes (rare w/ glottic CA)	Laryngoscopy CT/MRI	1° radiation 2° surgery 1° surgery for bulky T4 disease	5 yr survival: T4 >40% (surgery with radiation) Control rate early lesions >90% (radiation) 10 to 12% of small lesions fail radiotherapy
<b>Salivary Gland</b> Painless mass CN VII palsy Cervical lymphadenopathy Rapid growth Invasion of skin Constitutional signs/symptoms	FNA MRI/CT	1° surgery ± neck dissection: Post-op radiotherapy Chemotherapy if unresectable	Parotid: 10 yr survival: 85, 69, 43, and 14% for stages I to IV Submandibular: 2 yr survival: 82%, 5 year: 69% Minor salivary gland: 10 yr survival: 83, 52, 25, 23% for stages I to IV
<b>Thyroid</b> Thyroid mass, cervical nodes Vocal cord paralysis Hyper/hypothyroidism Dysphagia	FNA U/S	1° surgery I <sup>131</sup> for intermediate and high risk well differentiated thyroid cancer	Recurrences occur within 5 yr Need long-term f/u: clinical exam, thyroglobulin
<b>Parathyroid</b> Increased serum Ca <sup>2+</sup> Neck mass Bone disease, renal disease Pancreatitis	Sestamibi	Wide surgical excision Post-op monitoring of serum Ca <sup>2+</sup>	Recurrence rates 1 yr: 27% 5 yr: 82% 10 yr: 91% Mean survival: 6 to 7 yr

## Thyroid Carcinoma

**Table 17. Bethesda Classification of Thyroid Cytology**

Category	Risk of Malignancy
Non-diagnostic or unsatisfactory	Unknown
Benign	0-3%
Follicular lesion of undetermined significance/ Atypia of undetermined significance	5-15%
Follicular/Hurthle cell neoplasms	15-30%
Suspicious for malignancy	60-75%
Malignant	97-99%

**Table 18. Thyroid Carcinoma**

	Papillary	Follicular	Medullary	Anaplastic	Lymphoma
<b>Incidence</b> (% of all thyroid cancers)	70 to 75%	10%	3 to 5% (10% familial 90% sporadic)	<5%	<1%
<b>Route of Spread</b>	Lymphatic	Hematogenous	Lymphatic and hematogenous		
<b>Histology</b>	Orphan Annie nuclei Psammoma bodies Papillary architecture	Capsular/vascular invasion Invasion influences prognosis	Amyloid May secrete calcitonin, prostaglandins, ACTH, serotonin, kallikrein or bradykinin	Giant cells Spindle cells	
<b>Other</b>	Ps – Papillary cancer Popular (most common) Palpable lymph nodes Positive I <sup>131</sup> uptake Positive prognosis Post-op I <sup>131</sup> scan to guide treatments	Fs – Follicular cancer Far away mets Female (3:1) NOT FNA (can't be diagnosed by FNA) Favourable prognosis	Ms – Medullary cancer Multiple endocrine neoplasia (MEN IIa or IIb) aMyloid Median node dissection	More common in elderly 70% in women 20 to 30% have Hx of differentiated thyroid Ca (mostly papillary) or nodular goiter mass Rapidly enlarging neck Rule out lymphoma	Usually non-Hodgkin's lymphoma Rapidly enlarging thyroid mass Hx of Hashimoto's thyroiditis increases risk 60x 4:1 female predominance dysphagia, dyspnea, stridor, hoarseness, neck pain, facial edema, accompanied by "B" symptoms*
<b>Prognosis</b>	98% at 10 yr	92% at 10 yr	50% at 10 yr 20% at 10 yr if detected when clinically palpable	20 to 35% at 1 yr 13% at 10 yr	5 yr survival Stage IE 55%-80% Stage IIE 20%-50% Stage IIE/IV 15%-35%
<b>Treatment</b>	Small tumours: Near total thyroidectomy or lobectomy Diffuse/bilateral: Total thyroidectomy ± Post-op I <sup>131</sup> tx	Small tumours: Near total thyroidectomy/lobectomy/isthmectomy Large/diffuse tumours: Total thyroidectomy	Total thyroidectomy Median lymph node dissection if lateral cervical nodes +ve Modified neck dissection Post-op thyroxine Tracheostomy Screen asymptomatic relatives	Radiation and chemotherapy Small tumours: Total thyroidectomy ± external beam	Non-surgical Combined radiation Chemotherapy (CHOP**)

\*B symptoms = fever, night sweats, weight loss >10% in 6 mo

\*\* CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

### Approach to Thyroid Nodule

- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- any nodule >5 mm with suspicious sonographic features (particularly microcalcifications) should undergo FNA
- any nodule >1 cm should undergo FNA
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule

**Table 19. Management of the Thyroid Nodule**

Treatment	Indications
Radioiodine therapy	For the treatment of hyperthyroidism or as adjuvant treatment after surgery in the treatment of papillary or follicular carcinoma
Chemotherapy and/or radiotherapy	Anaplastic CA or thyroid lymphoma
Surgical excision	Mass that is "suspicious" on FNA Malignancy other than anaplastic CA or thyroid lymphoma Mass that on FNA is benign but increasing in size on serial imaging and/or >3-4 cm in size Hyperthyroidism not amenable to medical therapy

\*U/S findings: cystic: risk of malignancy <1%, solid: risk of malignancy approx. 10%, solid with cystic components: risk of malignancy same as if solid



**Indications for post-op radioactive iodine ablation – I<sup>131</sup>**  
Adjuvant therapy: decrease recurrent disease  
RAI therapy: treat persistent cancer

# Pediatric Otolaryngology



## Acute Otitis Media (AOM)

### Definition

- acute inflammation of middle ear

### Epidemiology

- 60 to 70% of children have at least 1 episode of AOM before 3 yr of age
- 18 mo to 6 yr most common age group
- peak incidence January to April
- one third of children have had  $\geq 3$  episodes by age 3

### Etiology

- *S. pneumoniae*: 35% of cases (incidence decreasing due to pneumococcus vaccine)
- *H. influenzae*: 25% of cases
- *M. catarrhalis*: 10% of cases
- *S. aureus* and *S. pyogenes* (all  $\beta$ -lactamase producing)
- anaerobes (newborns)
- Gram-negative enterics (infants)
- viral

### Predisposing Factors

- Eustachian tube dysfunction/obstruction:
  - swelling of tubal mucosa:
    - ♦ upper respiratory tract infection (URTI)
    - ♦ allergic rhinitis
    - ♦ chronic rhinosinusitis
  - obstruction/infiltration of Eustachian tube ostium:
    - ♦ tumour: nasopharyngeal carcinoma (adults)
    - ♦ adenoid hypertrophy (not due to obstruction but by maintaining a source of infection)
    - ♦ barotrauma (sudden changes in air pressure)
  - inadequate tensor palati function: cleft palate (even after repair)
  - abnormal Eustachian tube:
    - ♦ Down syndrome (horizontal position of Eustachian tube), Crouzon syndrome, and Apert syndrome
- disruption of action of:
  - cilia of Eustachian tube: Kartagener's syndrome
  - mucus secreting cells
  - capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, diabetes mellitus, hypogammaglobulinemia, cystic fibrosis

### Risk Factors

- bottle feeding, pacifier use
- second-hand smoke
- crowded living conditions (day care/group child care facilities) or sick contacts
- male
- family history

### Pathogenesis

- obstruction of Eustachian tube  $\rightarrow$  air absorbed in middle ear  $\rightarrow$  negative pressure (an irritant to middle ear mucosa)  $\rightarrow$  edema of mucosa with exudate/effusion  $\rightarrow$  infection of exudate from nasopharyngeal secretions

### Clinical Features

- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers
  - ear-tugging (this alone is not a good indicator of pathology)
  - hearing loss, balance disturbances (rare)
  - irritable, poor sleeping
  - vomiting and diarrhea
  - anorexia
- otoscopy of TM
  - hyperemia
  - bulging, pus may be seen behind TM
  - loss of landmarks: handle and long process of malleus not visible



#### Clinical Assessment of AOM in Paediatrics JAMA 2010;304:2161-2169

In assessment of AOM in paediatrics, ear pain is the most useful symptom with a likelihood ratio (LR) between 3.0 and 7.3. Useful otoscopic signs include erythematous (LR 8.4, 95% CI 7-11), cloudy (LR 3.4, 95% CI 2.8-4.2), bulging (LR 5.1, 95% CI 3.6-7.3), and immobile tympanic membrane on pneumatic otoscopy (LR 3.1, 95% CI 2.6-3.7).

## Diagnosis and Management

- American Academy of Pediatrics (AAP) Guidelines 2013 suggest the following action statements (adapted):
  - Diagnose AOM if:**
    - Moderate to severe bulging of TM or new onset of otorrhea not due to otitis externa
    - Mild bulging of tympanic membrane and recent (<48 h) ear pain or intense erythema of TM
    - Do not diagnose AOM if no middle ear effusion (based on pneumatic otoscopy or tympanometry)

## Management of AOM

- Assess for pain. If pain present, treat the pain
- For severe unilateral or bilateral AOM (moderate or severe otalgia, or otalgia for 48 h, or temperature 39°), prescribe antibiotics if 6 mo or older
- For nonsevere bilateral AOM (mild otalgia, otalgia <48 h, temperature <39°), prescribe antibiotics if 6 to 23 mo
- For nonsevere unilateral AOM, prescribe antibiotics or observe with close follow up based on joint decision making with parents if 6 to 23 mo
- For nonsevere unilateral or bilateral AOM, prescribe antibiotics or observe with close follow up based on joint decision making with parents if 24 mo or older
- Antibiotic treatment when given should consist of:
  - amoxicillin if child has not received amoxicillin in past 30 d, child does not have purulent conjunctivitis, or child is not allergic to penicillin
  - add  $\beta$ -lactamase coverage if received amoxicillin in past 30 d, has purulent conjunctivitis, or has history of recurrent AOM not responsive to amoxicillin
  - reassess if symptoms worsen or fail to respond to treatment within 48 to 72 h
  - do NOT prescribe prophylactic antibiotics to reduce frequency of AOM
- Tympanostomy tubes can be offered for recurrent AOM (3 episodes in 6 mo, 4 episodes in 1 yr) with 1 episode in preceding 6 mo
- Recommend pneumococcal vaccine and annual influenza vaccine to all children
- Encourage exclusive breastfeeding for at least 6 mo
- Avoid tobacco smoke

- antibiotic treatment hastens resolution: 10 d course
  - 1st line:
    - amoxicillin 80-90 mg/kg/d divided into two doses: safe, effective, and inexpensive
    - if penicillin allergic: macrolide (clarithromycin, azithromycin – high resistance), trimethoprim-sulphamethoxazole (Bactrim®)
  - 2nd line:
    - amoxicillin-clavulanic acid (Clavulin®)
    - cephalosporins: cefuroxime axetil (Ceftin®), ceftriaxone (Rocephin®), cefaclor (Ceclor®), cefixime (Suprax®)
    - AOM deemed unresponsive if clinical signs/symptoms and otoscopic findings persist beyond 48 h of antibiotic treatment
- symptomatic therapy:
  - antipyretics/analgesics (e.g. acetaminophen)
  - decongestants: may relieve nasal congestion but does not treat AOM
- prevention:
  - parent education about risk factors
  - antibiotic prophylaxis: amoxicillin or macrolide shown effective at half therapeutic dose
  - pneumococcal and influenza vaccine
  - surgery:
    - choice of surgical therapy for recurrent AOM depends on whether local factors (Eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinusitis) are responsible

## Complications of AOM

- otologic:
  - TM perforation
  - chronic suppurative OM
  - ossicular necrosis
  - cholesteatoma
  - persistent effusion (often leading to hearing loss)
- CNS:
  - meningitis
  - brain abscess
  - facial nerve paralysis
- other:
  - mastoiditis
  - labyrinthitis
  - sigmoid sinus thrombophlebitis



### Antibiotics for Acute Otitis Media in Children

Cochrane DB Syst Rev 2004;1:CD000219

**Study:** Meta-analysis of Randomized Controlled Trials (RCTs) on children (>6 mo) with acute otitis media comparing any antibiotic regime to placebo.  
**Data Sources:** Cochrane Central Register of Controlled Trials (2003 issue 1), MEDLINE (January 2000 to March 2003), and EMBASE (January 1990 to March 2003) without language restrictions.

**Main Outcomes:** 1) Pain at 24 h, and 2-7 d. 2) Hearing measured by tympanometry at 1 and 3 mo.

**Patients:** Pain: 24 h, 4 studies (n=717); 2-7 d 9 studies (n=2287). Hearing: 1 mo, 3 studies (n=472); 3 mo, 2 studies (n=370).

**Results:** Treatment with antibiotics had no significant impact on pain at 24 h. However, pain at 2-7 d was lower in the antibiotic groups with an NNT of 16 (p<0.00001). Antibiotics had no significant effect on hearing.

**Conclusion:** The role of antibiotics is largely restricted to pain control. This can also be achieved by analgesics. Therefore, parents should be counseled that other analgesics may be a safer option.



### Indications for Myringotomy and Tympanostomy Tubes in Recurrent AOM (RAOM) and OME

- Persistent OME >3 mo
- Lack of response to >3 mo of antibiotic therapy
- Persistent effusion for ≥3 mo after episode of AOM
- RAOM (>3 episodes in 6 mo, or >4 in 12 mo)
- Bilateral conductive hearing loss of >30 dB
- Chronic retraction of the tympanic membrane or pars flaccida
- Bilateral OME lasting >4 to 6 mo
- Craniofacial anomalies predisposing to middle ear infections (e.g. cleft palate)
- Complications of AOM or OME

Otolaryngologists' perceptions of the indications for tympanostomy tube insertion in children. *CMAJ* 2000;162:1285-1288

Clinical indicators myringotomy and tympanostomy tubes. American Academy of Otolaryngology – Head and Neck Surgery, 2010. Available at: <http://www.entnet.org/Practice/Myringotomy-and-Tympanostomy-tubes.cfm>



### Complications of Tympanostomy Tubes

#### Early

- Extrusion
- Blockage
- Persistent otorrhea

#### Late

- Myringosclerosis
- Persistent TM perforation
- Cholesteatoma

## Otitis Media with Effusion (OME)

### Definition

- presence of fluid in the middle ear without signs or symptoms of ear infection

### Epidemiology

- most common cause of pediatric hearing loss
- not exclusively a pediatric disease
- follows AOM frequently in children
- middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and 3+ mo in 10%

### Risk Factors

- same as AOM

### Clinical Features

- hearing loss  $\pm$  tinnitus
  - confirm with audiogram and tympanogram (flat) (see Figure 16B, OT10 and Figure 17B, OT11)
- fullness – blocked ear
- $\pm$  pain, low grade fever
- otoscopy of tympanic membrane:
  - discolouration – amber or dull grey with “glue” ear
  - meniscus fluid level behind TM
  - air bubbles
  - retraction pockets/TM atelectasis
  - most reliable finding with pneumotoscopy is immobility

### Treatment

- expectant: 90% resolve by 3 mo
- document hearing loss with audiogram
- no statistical proof that antihistamines, decongestants, antibiotics clear disease faster
- surgery: myringotomy  $\pm$  ventilation tubes  $\pm$  adenoidectomy (if enlarged or on insertion of second set of tubes after first set falls out)
- ventilation tubes to equalize pressure and drain ear

### Complications of Otitis Media with Effusion (OME)

- hearing loss, speech delay, learning problems in young children
- chronic mastoiditis
- ossicular erosion
- cholesteatoma especially when retraction pockets involve pars flaccida or postero-superior TM
- retraction of tympanic membrane, atelectasis, ossicular fixation

## Adenoid Hypertrophy

- size peaks at age 5 and resolves by age 12
- increase in size with repeated URTI and allergies

### Clinical Features

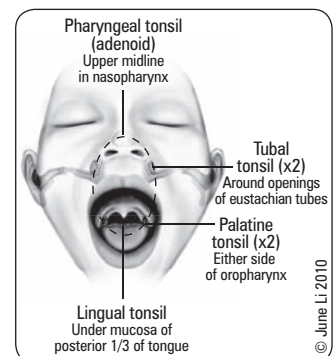
- nasal obstruction:
  - adenoid facies (open mouth, high arched palate, narrow midface, malocclusion)
  - history of hypernasal voice and snoring
  - long term mouth breather; minimal air escape through nose
- choanal obstruction:
  - chronic rhinosinusitis/rhinitis
  - obstructive sleep apnea
- chronic inflammation:
  - nasal discharge, post-nasal drip, and cough
  - cervical lymphadenopathy

### Diagnosis

- enlarged adenoids on nasopharyngeal exam (usually with flexible nasopharyngoscope)
- enlarged adenoid shadow on lateral soft tissue x-ray

### Complications

- Eustachian tube obstruction leading to serous otitis media
- interference with nasal breathing, necessitating mouth-breathing
- malocclusion
- sleep apnea/respiratory disturbance
- orofacial developmental abnormalities



**Figure 20. Waldeyer's ring**

An interrupted circle of protective lymphoid tissue at the upper ends of the respiratory and alimentary tracts



## Adenoidectomy

### Indications for Adenoidectomy

- chronic upper airway obstruction with sleep disturbance/apnea  $\pm$  cor pulmonale
- chronic nasopharyngitis resistant to medical treatment
- chronic serous otitis media and chronic suppurative otitis media (with 2nd set of tubes)
- recurrent acute otitis media resistant to antibiotics
- suspicion of nasopharyngeal malignancy
- persistent rhinorrhea

### Contraindications

- uncontrollable coagulopathy
- recent pharyngeal infection
- short or abnormal palate (cleft or false palate, zona pellucida)

### Complications

- bleeding, infection
- velopharyngeal insufficiency (hypernasal voice or nasal regurgitation)
- scarring of Eustachian tube orifice

## Sleep-Disordered Breathing in Children

### Definition

- spectrum of sleep-related breathing abnormalities ranging from snoring to OSA

### Epidemiology

- peak incidence between 2 and 8 yr when tonsils and adenoids are the largest relative to the pharyngeal airway

### Etiology

- due to a combination of anatomic and neuromuscular factors:
  - adenotonsillar hypertrophy
  - craniofacial abnormalities
  - neuromuscular hypotonia (i.e. cerebral palsy, Down syndrome)
  - obesity

### Clinical Features

- heavy snoring, mouth breathing, pauses or apnea, enuresis, excessive daytime sleepiness, behavioural/learning problems, diagnosis of ADHD, morning headache, failure to thrive

### Investigations

- flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
- polysomnography (obstructive apnea-hypopnea index  $>1/h$  considered abnormal)

### Treatment

- surgical: bilateral tonsillectomy and adenoidectomy
- nonsurgical: CPAP, BiPAP, sleep hygiene

## Acute Tonsillitis

### Etiology

- Group A  $\beta$ -hemolytic *streptococci* (most common) and Group C or G *streptococci*
- *S. pneumoniae*, *S. aureus*, *H. influenzae*, *M. catarrhalis*
- EBV

### Clinical Features

- symptoms:
  - sore throat
  - dysphagia, odynophagia, trismus
  - malaise, fever
  - otalgia (referred)
- signs:
  - tender cervical lymphadenopathy, especially submandibular, jugulodigastric
  - tonsils enlarged, inflammation  $\pm$  exudates/white follicles
  - strawberry tongue, scarlatiniform rash (scarlet fever)
  - palatal petechiae (infectious mononucleosis)



**Trismus:** motor disturbance of the trigeminal nerve, leading to spasm of the muscles of mastication, with difficulty in opening the mouth (lockjaw).



**DDx Sore Throat**

- Streptococcal pharyngitis
- Viral pharyngitis
- Infectious mononucleosis
- Tonsillitis
- Peritonsillar abscess
- Foreign body/trauma
- Leukemia
- Hodgkin's disease

**Investigations**

- CBC
- swab for C&S
- latex agglutination tests
- Monospot® – less reliable in children <2 yr old

**Treatment**

- soft diet, ample fluid intake
- gargle with warm saline solution
- analgesics and antipyretics
- antibiotics:
  - only after appropriate swab for C&S
  - 1st line penicillin or amoxicillin (erythromycin if penicillin allergy) x 10 d
  - rheumatic fever risk emerges approximately 9 d after the onset of symptoms:
    - ♦ antibiotics are utilized mainly to avoid this serious sequela and to provide earlier symptomatic relief
  - no evidence for the role of antibiotics in the avoidance of post-streptococcal glomerulonephritis

**Complications of Tonsillitis**

- Rheumatic heart disease
- Arthritis
- Scarlet fever
- Peritonsillar abscess (Quinsy), intratonsillar
- Deep neck space infection
- Sepsis
- Glomerulonephritis

## Peritonsillar Abscess (Quinsy)

**Definition**

- cellulitis of space behind tonsillar capsule extending onto soft palate leading to abscess

**Etiology**

- bacterial: Group A strep (GAS) (50% of cases), *S. pyogenes*, *S. aureus*, *H. influenzae*, and anaerobes

**Epidemiology**

- can develop from acute tonsillitis with infection spreading into plane of tonsillar bed
- unilateral
- most common in 15 to 30 yr old age group

**Clinical Features**

- fever and dehydration
- sore throat, dysphagia, and odynophagia
- extensive peritonsillar swelling but tonsil may appear normal
- edema of soft palate
- uvular deviation
- involvement of motor branch of CN V (can lead to trismus)
- dysphonia (edema → failure to elevate palate) 2° to CN X involvement
- unilateral referred otalgia
- cervical lymphadenitis

**Complications**

- aspiration pneumonia 2° to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

**Treatment**

- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 d if cultures positive for GAS
- add PO/IV metronidazole or clindamycin x 10 d if culture positive for *Bacteroides*
- consider tonsillectomy after second episode

**Other Parapharyngeal Space Infection**

- pharyngitis
- parotitis (see *Salivary Glands*, OT29)
- otitis
- mastoiditis (Bezold's abscess)
- odontogenic infection

**Quinsy Triad**

- Trismus
- Uvular deviation
- Dysphonia ("hot potato voice")

## Tonsillectomy

### Absolute Indications

- most common indication: sleep-disordered breathing
- 2nd most common indication: recurrent throat infections
- tonsillar hypertrophy causing upper airway obstruction, obstructive sleep apnea, severe dysphagia, or cardiopulmonary complications such as cor pulmonale
- suspicion of malignancy (e.g. lymphoma, squamous cell carcinoma)
- orofacial/dental deformity
- hemorrhagic tonsillitis

### Relative Indications (to reduce disease burden)

- recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 yr, or at least 3 episodes per year for 3 yr, with documentation in the medical record for each episode of sore throat and 1 or more of the following: temperature  $>38.3^{\circ}\text{C}$ , cervical adenopathy, tonsillar exudate, or positive test for Group A  $\beta$ -hemolytic *streptococcus* (Paradise Criteria)
- chronic tonsillitis with halitosis (bad breath) or sore throat  $\pm$  tonsilloliths (clusters of calcified material that form in the crevices of the tonsils)
- complications of tonsillitis: quinsy/peritonsillar abscess, parapharyngeal abscess, retropharyngeal abscess
- failure to thrive

### Relative Contraindications

- velopharyngeal insufficiency: overt or submucous/covert cleft of palate, impaired palatal function due to neurological or neuro-muscular abnormalities
- hematologic: coagulopathy, anemia
- infectious: active local infection without urgent obstructive symptoms

### Complications

- hemorrhage: early – within 24 h; delayed – 7-10 d
- odynophagia and/or otalgia; dehydration 2° to odynophagia
- infection
- atlantoaxial subluxation (Grisel's syndrome): rare

## Airway Problems in Children

### DIFFERENTIAL DIAGNOSIS BY AGE GROUP

#### Neonates (obligate nose breathers)

- extralaryngeal:
  - choanal atresia (e.g. CHARGE syndrome)
  - nasopharyngeal dermoid, glioma, encephalocele
  - glossoptosis: Pierre-Robin sequence, Down syndrome, lymphatic malformation, hemangioma
- laryngeal:
  - laryngomalacia: most common cause of stridor in children
  - laryngocele
  - vocal cord palsy (due to trauma or Arnold-Chiari malformation)
  - glottic web
  - subglottic stenosis
  - laryngeal cleft
- tracheal:
  - tracheoesophageal fistula
  - tracheomalacia
  - vascular rings

#### 2 to 3 Months

- congenital:
  - laryngomalacia
  - vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
  - laryngeal papilloma
- acquired:
  - subglottic stenosis: post intubation
  - tracheal granulation: post intubation
  - tracheomalacia: post tracheotomy and TEF repair

**Infants – Sudden Onset**

- foreign body aspiration
- croup
- bacterial tracheitis
- caustic ingestion
- epiglottitis

**Children and Adults**

- infection:
  - Ludwig's angina
  - peritonsillar/parapharyngeal abscess
  - retropharyngeal abscess
- neoplastic:
  - squamous cell carcinoma (SCC) (adults): larynx, hypopharynx
  - retropharyngeal: lymphoma, neuroblastoma
  - nasopharyngeal: carcinoma, rhabdomyosarcoma
- allergic:
  - angioneurotic edema
  - polyps (suspect cystic fibrosis in children)
- trauma:
  - laryngeal fracture, facial fracture
  - burns and lacerations
  - post-intubation
  - caustic ingestion
- congenital:
  - lingual thyroid/tonsil

## Signs of Airway Obstruction

**Stridor**

- note quality, timing (inspiratory or expiratory)
- body position important:
  - lying prone: subglottic hemangioma, double aortic arch
  - lying supine: laryngomalacia, glossoptosis
- site of stenosis:
  - vocal cords or above: inspiratory stridor
  - subglottis and extrathoracic trachea: biphasic stridor
  - distal tracheobronchial tree: expiratory stridor

**Respiratory Distress**

- nasal flaring
- supraclavicular and intercostal indrawing
- sternal retractions
- use of accessory muscles of respiration
- tachypnea
- cyanosis
- altered LOC

**Feeding Difficulty and Aspiration**

- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- laryngeal cleft g aspiration pneumonia
- TEF

## Acute Laryngotracheobronchitis (Croup)

- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining and associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

**Etiology**

- viral: parainfluenzae I (most common), II, III, influenza A and B, RSV

**Signs of Croup****The 3 Ss**

Stridor  
Subglottic swelling  
Seal bark cough

**Clinical Features**

- age: 4 mo to 5 yr
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea-lion bark)
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- “steeples-sign” on AP x-ray of neck
- if recurrent croup, think subglottic stenosis

**Treatment**

- racemic epinephrine via nebulizer q1-2h, prn (only if in respiratory distress)
- systemic corticosteroids (e.g. dexamethasone, prednisone)
- adequate hydration
- close observation for 3 to 4 h
- intubation if severe
- hospitalize if poor response to steroids after 4 h and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)
- if recurrent episodes of croup-like symptoms, consider bronchoscopy several weeks after acute episode settles to rule out underlying subglottic stenosis

## Acute Epiglottitis

- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

**Etiology**

- *H. influenzae* type B
- relatively uncommon condition due to Hib vaccine

**Clinical Features**

- any age, most commonly 1 to 4 yr
- rapid onset
- toxic-looking, fever, anorexia, restlessness
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up, open mouth, drooling, tongue protruding, sore throat, dysphagia

**Investigations and Management**

- investigations and physical examination may lead to complete obstruction, thus preparations for intubation or tracheotomy must be made prior to any manipulation
- stat ENT/anesthesia consult(s)
- WBC (elevated), blood and pharyngeal cultures after intubation
- lateral neck radiograph (only done if patient stable)

**Treatment**

- secure airway
- IV access with hydration
- antibiotics: IV cefuroxime, cefotaxime, or ceftriaxone
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis



Acute epiglottitis is a medical emergency.



When managing epiglottitis, it is important not to agitate the child, as this may precipitate complete obstruction.



**Thumb sign:** cherry-shaped epiglottic swelling seen on lateral neck radiograph.

## Subglottic Stenosis

**Congenital**

- diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage)

**Acquired**

- following prolonged, repeated or traumatic intubation:
  - most commonly due to endotracheal intubation; nasal intubation is less traumatic and preferred in long term intubation as it puts less pressure on the subglottis (tube sits at different orientation) and there is less movement
  - subglottic stenosis is related to duration of intubation and pressure of the endotracheal tube cuff
- can also be due to foreign body, infection (e.g. TB, diphtheria, syphilis) or chemical irritation

**Clinical Features**

- biphasic stridor
- respiratory distress
- recurrent/prolonged croup

**Diagnosis**

- rigid laryngoscopy and bronchoscopy

**Treatment**

- if soft stenosis: divide tissue with knife or laser, dilate with balloon  $\pm$  steroids
- if firm stenosis: laryngotracheoplasty

## Laryngomalacia

- short aryepiglottic folds, omega-shaped epiglottis, pendulous mucosa
- caused by indrawing of supraglottis on inspiration leading to laryngopharyngeal reflux of acid

**Clinical Features**

- high-pitched inspiratory stridor at 1 to 2 wk
- constant or intermittent and more pronounced supine
- usually mild but when severe can be associated with cyanosis or feeding difficulties, leading to failure to thrive

**Treatment**

- observation is usually sufficient as symptoms spontaneously subside by 12 to 18 mo in >90% of cases
- in the case of severe laryngomalacia, division of the aryepiglottic folds (supraglottoplasty) provides relief



Laryngomalacia is the most common cause of stridor in infants.

## Foreign Body

**Ingested**

- usually stuck at cricopharyngeus
- coins, toys, batteries (emergency)
- presents with drooling, dysphagia, stridor if very large

**Aspirated**

- usually stuck at right mainstem bronchus
- peanuts, carrot, apple core, popcorn, balloons
- presentation
  - stridor if lodged in trachea
  - unilateral "asthma" if bronchial, therefore often misdiagnosed as asthma
  - if totally occludes airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax, death



Foreign body inhalation is the most common cause of accidental death in children.

**Diagnosis and Treatment**

- any patient with suspected foreign body should be kept NPO immediately
- inspiration-expiration chest x-ray (if patient is stable)
- bronchoscopy or esophagoscopy with removal
- rapid onset, not necessarily febrile or elevated WBC



Batteries MUST be ruled out as a foreign body (vs. coins) as they are lethal and can erode through the esophagus. Batteries have a halo sign around the rim on AP xray and a step deformity on lateral xray.

## Deep Neck Space Infection

- most commonly arise from an infection of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
- often a rapid onset and may progress to fatal complications

**Etiology**

- usually mixed aerobes and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes



Trismus means the pterygoids are involved and airway will become increasingly hard to access.

**Clinical Features**

- sore throat or pain and trismus
- dysphagia and odynophagia
- stridor and dyspnea
- late findings may include dysphonia and hoarseness
- swelling of the face and neck, erythema
- asymmetry of the oropharynx with purulent oral discharge
- lymphadenopathy



These investigations should be obtained carefully and the surgeon should consider accompanying the patient as the worst place to lose an airway is during imaging.

**Diagnosis**

- lateral cervical view plain radiograph
- CT
- MRI



Ludwig's angina is the prototypical infection of the submandibular and sublingual space.

**Treatment**

- secure the airway
- surgical drainage
- maximum doses of IV systemic antimicrobials regimens according to the site of infection



# Common Medications

Table 20. Antibiotics

Generic Name (Brand Name)	Dose	Indications	Notes
amoxicillin (Amoxil <sup>®</sup> , Amoxi <sup>®</sup> , Amox <sup>®</sup> )	Adult: 500 mg PO tid Children: 80-90 mg/kg/d in 2 divided doses	<i>Streptococcus</i> , <i>Pneumococcus</i> , <i>H. influenzae</i> , Proteus coverage	May cause rash in patients with infectious mononucleosis
piperacillin with tazobactam (Zosyn <sup>®</sup> )	3 g PO q6h	Gram-positive and negative aerobes and anaerobes plus <i>Pseudomonas</i> coverage	May cause pseudomembranous colitis
ciprofloxacin (Cipro <sup>®</sup> , Ciloxan <sup>®</sup> )	500 mg PO bid	<i>Pseudomonas</i> , <i>Streptococci</i> , MRSA, and most Gram-negative; no anaerobic coverage	Do not give systemic quinolones to children
erythromycin (Erythrocin <sup>®</sup> , EryPed <sup>®</sup> , Staticin <sup>®</sup> , T-Stat <sup>®</sup> , Erybid <sup>®</sup> , Novorythro Encap <sup>®</sup> )	500 mg PO qid	Alternative to penicillin	Ototoxic

Table 21. Otic Drops

Generic Name (Brand Name)	Dose	Indications	Notes
ciprofloxacin (Ciprodex <sup>®</sup> )	4 gtt in affected ear bid	For otitis externa and complications of otitis media <i>Pseudomonas</i> , <i>Streptococci</i> , MRSA, and most Gram-negative; no anaerobic coverage	
neomycin, polymyxin B sulfate, and hydrocortisone (Cortisporin Otic <sup>®</sup> )	5 gtt in affected ear tid	For otitis externa Used for inflammatory conditions which are currently infected or at risk of bacterial infections	May cause hearing loss if placed in inner ear
hydrocortisone and acetic acid (VoSol HC <sup>®</sup> )	5-10 gtt in affected ear tid	For otitis media	Bactericidal by lowering pH
tobramycin and dexamethasone (TobraDex <sup>®</sup> )	5-10 gtt in affected ear bid	For chronic suppurative otitis media	Risk of vestibular or cochlear toxicity

Table 22. Nasal Sprays

Generic Name (Brand Name)	Indications	Notes
<b>Steroid</b>		
flunisolide (Rhinalar <sup>®</sup> ) budesonide (Rhinocort <sup>®</sup> ) triamcinolone (Nasacort <sup>®</sup> ) beclomethasone (Beconase <sup>®</sup> ) mometasone furoate, monohydrate (Nasonex <sup>®</sup> ) fluticasone furoate (Avamys <sup>®</sup> )	Allergic rhinitis Chronic sinusitis	Requires up to 4 wk of consistent use to have effect Long term use Dries nasal mucosa; get minor bleeding Patient should stop if epistaxis May sting Flonase <sup>®</sup> and Nasonex <sup>®</sup> not absorbed systemically
<b>Antihistamine</b>		
levocarbastine (Livostin <sup>®</sup> )	Allergic rhinitis	Immediate effect If no effect by 3 d then discontinue Use during allergy season
<b>Decongestant</b>		
xylometazoline (Otrivin <sup>®</sup> ) oxymetazoline (Dristan <sup>®</sup> ) phenylephrine (Neosynephrine <sup>®</sup> )	Acute sinusitis Rhinitis	Careful if patient has hypertension Short term use (<5 d) If long term use, can cause decongestant addiction (i.e. rhinitis medicamentosa)
<b>Antibiotic/Decongestant</b>		
framycetin, gramicidin, phenylephrine (Soframycin <sup>®</sup> )	Acute sinusitis	
<b>Anticholinergic</b>		
ipratropium bromide (Atrovent <sup>®</sup> )	Vasomotor rhinitis	Careful not to spray into eyes as can cause burning or precipitation of narrow angle glaucoma Increased rate of epistaxis when combined with topical nasal steroids
<b>Lubricants</b>		
saline, NeilMed <sup>®</sup> , Rhinaris <sup>®</sup> , Secaris <sup>®</sup> , Polysporin <sup>®</sup> , Vaseline <sup>®</sup>	Dry nasal mucosa	Use prn Rhinaris <sup>®</sup> and Secaris <sup>®</sup> may cause stinging

Source: Dr. M. M. Carr

## References

### Textbooks

- Bailey BJ. Head and neck surgery-otolaryngology, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 1998.
- Becker W, Naumann HH, Pfaltz CR. Ear, nose, and throat diseases, 2nd ed. New York: Thieme Medical Publishers, 1994.
- Dhillon RS, East CA. Ear, nose, and throat, and head and neck surgery: an illustrated colour text, 2nd ed. New York: Churchill & Livingston, 1999.
- Jafek BW, Murrow BW. ENT secrets, 2nd ed. Philadelphia: Hanley & Belfus, 2001.
- Lee KJ (ed). Essential otolaryngology: head and neck surgery, 8th ed. New York: McGraw-Hill, 2003.
- Lucente FE, Har-El G (editors). Essentials of otolaryngology, 4th ed. Philadelphia: Lippincott Williams and Wilkins, 1999.
- Layland MK (ed). Washington manual otolaryngology survival guide. Philadelphia: Lippincott Williams and Wilkins, 2003.
- Pasha R. Otolaryngology head and neck surgery clinical reference guide, 3rd ed. San Diego: Plural Publishing, 2010.

### Journal Articles

- American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium. Committee on hearing and equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease. *Otolaryngol Head and Neck Surg* 1995;113:181-185.
- Ang K, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *NEJM* 2010;363:24-35.
- Berman S. Current concepts: otitis media in children. *NEJM* 1995;332:1560-1565.
- Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *NEJM* 2006;354:567-568.
- Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systemic review. *JAMA* 2010;304:2161-169.
- Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167-1214.
- Desrosiers M, Evans GA, Keith PK, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *Allergy Asthma Clin Immunol* 2011;7:2.
- D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *NEJM* 2007;356:1944-1956.
- Fakhry C, Westra WH, Li S, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst* 2008;100:261-269.
- Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. *NEJM* 2001;345:1890-1900.
- Furman JM, Cass SP. Benign paroxysmal positional vertigo. *NEJM* 1999;341:1590-6.
- Glasziou PP, Del Mar CB, Sanders SL, et al. Antibiotics for acute otitis media in children. *Cochrane DB Syst Rev* 2004;1:CD000219.
- Grégoire V, Maignon P. Intensity modulated radiation therapy in head and neck squamous cell carcinoma: state of the art and future challenges. *Cancer Radiother* 2005;9:42-50.
- Hilton M, Pinder D. The Epley (canalith repositioning) maneuver for benign paroxysmal positional vertigo. *Cochrane ear, nose, and throat disorders group. Cochrane DB Syst Rev* 2004;Issue 4.
- Jackson CG, von Doersten PG. The facial nerve: current trends in diagnosis, treatment, and rehabilitation. *Otolaryngol for Internist* 1999;83:179-195.
- Li X, Gao L, Li H, Gao J, et al. Human papillomavirus infection and laryngeal cancer risk: a systemic review and meta-analysis. *J Infect Dis* 2013;207:479-488.
- Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and treatment of acute otitis media. *Pediatrics* 2013;e964-e999.
- Low DE, Desrosiers M, McSherry J, et al. A practical guide for the diagnosis and treatment of acute sinusitis. *CMAJ* 1997;156:S1-14.
- MacCallum PL, Parnes LS, Sharpe MD, Harris C. Comparison of open, percutaneous and translaryngeal tracheostomies. *Otolaryngol Head Neck Surg* 2000;122:686-690.
- McIsaac WJ, Coyte PC, Croxford R, et al. Otolaryngologists' perceptions of the indications for tympanostomy tube insertion in children. *CMAJ* 2000;162:1285-1288.
- Strafford ND, Wilde A. Parotid cancer. *Surg Oncol* 1997;6:209-213.

Tanvi Agarwal, Nicole Fischer, Suparna Sharma and Wallace Wee, chapter editors  
 Maria Jogova and Howard Meng, associate editors  
 Melini Gupta, EBM editor  
 Dr. Nirit Bernhard, Dr. Sohail Cheema, Dr. Steven Moss, Dr. Sharon Naymark and  
 Dr. Angela Punnett, staff editors

<b>Acronyms</b> .....	<b>3</b>	<b>Gastroenterology</b> .....	<b>34</b>
<b>Pediatric Quick Reference Values</b> .....	<b>3</b>	Vomiting	
<b>Primary Care</b> .....	<b>3</b>	Gastroesophageal Reflux	
Visit Overview		Tracheoesophageal Fistula (TEF)	
Routine Immunization		Pyloric Stenosis	
Vaccine Administration		Duodenal Atresia	
Growth and Development		Malrotation of the Intestine	
Nutrition		Diarrhea	
Injury Prevention Counselling		Infective Diarrhea	
<b>Common Complaints</b> .....	<b>8</b>	Toddler's Diarrhea	
Breath-Holding Spells		Lactase Deficiency (Lactose Intolerance)	
Circumcision		Irritable Bowel Syndrome	
Crying/Fussing Child		Celiac Disease	
Dentition and Caries		Milk Protein Allergy	
Enuresis		Inflammatory Bowel Disease (IBD)	
Encopresis		Cystic Fibrosis	
Failure to Thrive		Constipation	
Infantile Colic		Abdominal Pain	
Obesity		Chronic Abdominal Pain	
Poison Prevention		Abdominal Mass	
Rashes		Upper Gastrointestinal Bleeding	
Sleep Disturbances		Lower Gastrointestinal Bleeding	
Toilet Training		<b>Genetics, Dysmorphisms and Metabolism</b> ...	<b>41</b>
Sudden Infant Death Syndrome (SIDS)		Genetic Anomalies	
<b>Child Abuse and Neglect</b> .....	<b>14</b>	Approach to the Dysmorphic Child	
Physical Abuse		Genetics	
Sexual Abuse		Genetic Syndromes	
Neglect		Muscular Dystrophy (MD)	
<b>Adolescent Medicine</b> .....	<b>15</b>	Metabolic Disease	
<b>Cardiology</b> .....	<b>16</b>	Phenylketonuria (PKU)	
Congenital Heart Disease (CHD)		Galactosemia	
Acyanotic Congenital Heart Disease		<b>Hematology</b> .....	<b>46</b>
Cyanotic Congenital Heart Disease		Approach to Anemia	
Congestive Heart Failure (CHF)		Physiologic Anemia	
Dysrhythmias		Iron Deficiency Anemia	
Heart Murmurs		Anemia of Chronic Disease	
Infective Endocarditis		Sickle Cell Disease (SCD)	
<b>Development</b> .....	<b>22</b>	Thalassemia	
Approach to Global Developmental Delay		Hereditary Spherocytosis	
Intellectual Disability		Glucose-6-Phosphate Dehydrogenase (GP6)	
Language Delay		Deficiency	
Fetal Alcohol Spectrum Disorder (FASD)		Bleeding Disorders	
Learning Disabilities		Immune Thrombocytopenic Purpura (ITP)	
Motor Delay		Hemophilia	
<b>Endocrinology</b> .....	<b>26</b>	von Willebrand's Disease	
Anti-Diuretic Hormone		<b>Oncology</b> .....	<b>50</b>
Diabetes Mellitus (DM)		Leukemia	
Growth		Lymphoma	
Hypercalcemia/Hypocalcemia/Rickets		Brain Tumours	
Hyperthyroidism and Hypothyroidism		Wilms' Tumour (Nephroblastoma)	
Sexual Development		Neuroblastoma	
		Bone Tumours	
		Febrile Neutropenia	
		Tumour Lysis Syndrome	
		Hyperleukocytosis	
		Lymphadenopathy	

<b>Infectious Diseases</b> . . . . .	<b>54</b>	Slipped Capital Femoral Epiphysis	
Fever		Developmental Dysplasia of the Hip	
Acute Otitis Media (AOM)		Legg-Calve-Perthes Disease	
Diphtheria		Osgood-Schlatter Disease	
Gastroenteritis		Congenital Talipes Equinovarus (Club Foot)	
HIV Infection		Scoliosis	
Infectious Pediatric Exanthems			
Infectious Mononucleosis		<b>Otolaryngology</b> . . . . .	<b>OT38</b>
Infectious Pharyngitis/Tonsillitis		Acute Otitis Media (AOM)	
Meningitis		Otitis Media with Effusion (OME)	
Mumps		Adenoid Hypertrophy	
Pertussis		Adenoidectomy	
Pneumonia		Sleep-Disordered Breathing	
Periorbital (Preseptal) and Orbital Cellulitis		Acute Tonsillitis	
Sexually Transmitted Infection		Peritonsillar Abscess (Quinsy)	
Sinusitis		Tonsillectomy	
Urinary Tract Infection (UTI)		Airway Problems	
		Signs of Airway Obstruction	
<b>Neonatology</b> . . . . .	<b>66</b>	Acute Laryngotracheobronchitis (Croup)	
Gestational Age (GA) and Size		Acute Epiglottitis	
Routine Neonatal Care		Subglottic Stenosis	
Neonatal Resuscitation		Laryngomalacia	
Approach to the Depressed Newborn		Foreign Body	
		Deep Neck Space Infection	
<b>Common Conditions of Neonates</b> . . . . .	<b>69</b>	<b>Plastic Surgery</b> . . . . .	<b>PL34</b>
Apnea		Craniofacial Anomalies	
Bleeding Disorders in Neonates		Congenital Hand Anomalies	
Bronchopulmonary Dysplasia (BPD)			
Cyanosis		<b>Psychiatry</b> . . . . .	<b>PS33</b>
Diaphragmatic Hernia		The Child Psychiatric Interview	
Hypoglycemia		Developmental Concepts	
Intraventricular Hemorrhage (IVH)		Mood Disorders	
Jaundice		Anxiety Disorders	
Necrotizing Enterocolitis (NEC)		Childhood Schizophrenia	
Persistent Pulmonary Hypertension of the Newborn (PPHN)		Pervasive Developmental Disorders	
Respiratory Distress in the Newborn		Attention Deficit Hyperactivity Disorder	
Retinopathy of Prematurity (ROP)		Oppositional Defiant Disorder	
Common Neonatal Skin Conditions		Conduct Disorder	
Sepsis in the Neonate			
<b>Nephrology</b> . . . . .	<b>79</b>	<b>Respirology</b> . . . . .	<b>92</b>
Approach to Infant/Child with Dehydration		Approach to Dyspnea	
Common Pediatric Renal Disease		Upper Respiratory Tract Diseases	
Hemolytic Uremic Syndrome (HUS)		Lower Respiratory Tract Diseases	
Nephritic Syndrome		Pneumonia	
Nephrotic Syndrome		Bronchiolitis	
Hypertension in Childhood		Asthma	
		Cystic Fibrosis (CF)	
<b>Neurology</b> . . . . .	<b>86</b>	<b>Rheumatology</b> . . . . .	<b>96</b>
Seizure Disorders		Evaluation of Limb Pain	
Febrile Seizures		Growing Pains	
Recurrent Headache		Transient Synovitis of the Hip	
Hypotonia		Septic Arthritis	
Cerebral Palsy (CP)		Juvenile Idiopathic Arthritis (JIA)	
Neurocutaneous Syndromes		Reactive Arthritis	
Acute Disseminated Encephalomyelitis (ADEM)		Lyme Arthritis	
		Systemic Lupus Erythematosus (SLE)	
<b>Neurosurgery</b> . . . . .	<b>NS35</b>	Vasculitides	
Spinal Dysraphism			
Hydrocephalus		<b>Urology</b> . . . . .	<b>U36</b>
Dandy-Walker Malformation		Congenital Abnormalities	
Chiari Malformations		Nephroblastoma (Wilms' Tumour)	
Craniosynostosis		Cryptorchidism/Ectopic Testes	
Brain Tumours		Disorders of Sexual Differentiation (DSD)	
		Circumcision	
<b>Orthopedics</b> . . . . .	<b>OR38</b>	<b>Common Medications</b> . . . . .	<b>100</b>
Fractures in Children		<b>References</b> . . . . .	<b>101</b>
Stress Fractures			
Epiphyseal Injury			

## Pediatric Quick Reference Values

**Table 1. Average Vitals at Various Ages**

Age	Pulse (bpm)	Respiratory Rate (br/min)	sBP (mmHg)
Neonate	90-170	40-60	70-90
3-12 months	80-165	30-55	80-100
1-2 years	80-125	25-45	90-100
3-11 years	70-115	18-30	100-110
12-15 years	60-100	12-18	110-130

## Primary Care

### Visit Overview

- schedule:
  - newborn (within 1 wk post-discharge), 1, 2, 4, 6, 9, 12, 15, 18, 24 mo
  - annually between age 2 to 6; every other year between age 6 to 11
- content:
  - history and physical exam including growth, development, and nutrition
  - routine immunization
  - counseling and anticipatory guidance

### Routine Immunization

**Table 2. Publicly Funded Immunization Schedule for Ontario, August 2011**

Age	DTaP-IPV-Hib	dTaP-IPV	Pneu-C-13	Rot-1	Men-C-C	MMR	Var	MMRV	Men-C-ACYW	HepB	HPV-4	Tdap	Inf
2 months	✓IM		✓IM	✓PO									
4 months	✓IM		✓IM	✓PO									
6 months	✓IM												
12 months			✓IM		✓IM	✓SC							
15 months							✓SC						
18 months	✓IM												
4-6 years		✓IM						✓SC					
Grade 7									✓IM	✓IM			
Grade 8 female											✓IM		
14-16 years												✓IM	
Every autumn													✓IM

IM = intramuscular; PO = per oral; SC = subcutaneous

## Acronyms

AAP	American Association of Pediatricians
ALPS	autoimmune lymphoproliferative syndrome
AOM	acute otitis media
ARND	alcohol-related neurodevelopmental disorder
ASD	atrial septal defect
ASOT	antistreptolysin-o-titre
ATN	acute tubular necrosis
CAS	Children's Aid Society
CF	cystic fibrosis
CHD	congenital heart defect
CMV	cytomegalovirus
CP	cerebral palsy
CPS	Canadian Pediatric Society
DI	diabetes insipidus
DIC	disseminated intravascular coagulopathy
DM	diabetes mellitus
DS	Down syndrome
EBV	Epstein-Barr virus
FASD	fetal alcohol spectrum disorder
FSH	follicle stimulating hormone
FTT	failure to thrive
GA	gestational age
GERD	gastroesophageal reflux disease
GH	growth hormone
GN	glomerulonephritis
HIE	hypoxic ischemic encephalopathy
HSP	Henoch-Schönlein purpura
HUS	hemolytic uremic syndrome
IBW	ideal body weight
ICH	intracranial hemorrhage
IUGR	intra-uterine growth retardation
IVH	intraventricular hemorrhage
IVIg	intravenous immunoglobulin
LH	luteinizing hormone
LLSB	lower left sternal border
LOC	level of consciousness
LP	lumbar puncture
LRTI	lower respiratory tract infection
NICU	neonatal intensive care unit
PDA	patent ductus arteriosus
PKU	phenylketonuria
PUVA	psoralen + UVA
RDS	respiratory distress syndrome
RUSB	right upper sternal border
SEM	systolic ejection murmur
SLE	systemic lupus erythematosus
TPN	total parenteral nutrition
UMN	upper motor neuron
URTI	upper respiratory tract infection
UVA	ultraviolet
VSD	ventricular septal defect

**Table 2. Publicly Funded Immunization Schedule for Ontario, August 2011** (continued)

Vaccine	Adverse Reaction	Contraindication
DTaP-IPV	Prolonged crying Hypotonic unresponsive state (rare) Seizure on day of vaccine (rare)	Evolving unstable neurologic disease Hyporesponsive/hypotonic following previous vaccine Anaphylactic reaction to neomycin or streptomycin
Rot-1	Cough Diarrhea, vomiting	History of intussusception Immunocompromised Abdominal disorder (e.g. Meckel's diverticulum) Received blood products (e.g. immunoglobulin) within 42 d
MMR	Measle-like rash (7-14d) Lymphadenopathy, arthralgia, arthritis Parotitis (rare) Especially painful injection	Pregnancy Immunocompromised infants (except healthy HIV positive children) Anaphylactic reaction to gelatin
Var	Mild varicella-like papules or vesicles	Pregnant or planning to get pregnant within 3 mo Anaphylactic reaction to gelatin
HepB		Anaphylactic reaction to Baker's yeast
MMRV	Same as MMR and Var vaccines	Same as MMR and Var vaccines
dTAP		1st trimester pregnancy
Inf	Malaise, myalgia Febrile seizure Hypersensitivity reaction	Egg-allergic individuals – unless the risk of the disease outweighs the small risk of a systemic hypersensitivity reaction. Referral to an allergy specialist is recommended, as vaccination might be possible after careful evaluation, skin testing and graded challenge or desensitization.
HPV-4	Pruritis	

DTaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (i.e. Pentacel<sup>®</sup>, Pentavax<sup>®</sup>); Hib = *hemophilus influenza* type b conjugate vaccine; Pneu-C-13 = pneumococcal 13-valent conjugate vaccine; Rot-1 = rotavirus oral vaccine; MMR = measles, mumps, rubella vaccine; Men-C-C = meningococcal c conjugate vaccine; Var = varicella vaccine; HepB = hepatitis b vaccine; MMRV = measles, mumps, rubella, varicella vaccine; dTAP = diphtheria, tetanus, acellular pertussis vaccine; Inf = influenza vaccine; HPV-4 = human papilloma virus vaccine

**Any Vaccine:****Adverse Reactions**

**Local:** induration, tenderness, redness, swelling

**Systemic:** fever, rash, irritability

**Allergic:** urticaria, rhinitis, anaphylaxis

**Contraindications**

Moderate/severe illness  $\pm$  fever

Allergy to vaccine component

No need to delay vaccination for mild URTI

**Canadian Immunization Guide**

National Advisory Committee on Immunization. Canadian Immunization Guide (CIG), 2006, 7th edition. Public Health Agency of Canada, 2006. Available at: <http://www.phac-aspc.gc.ca/publicat/cig-gci/>

**Vaccination in Cases of Asplenia or Hyposplenia (such as Sickle Cell Disease)**

- Should receive all routine immunizations, including the yearly influenza vaccine
- No vaccines are contraindicated
- Susceptible to infection by encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, *N. meningitidis*)
- For meningococcal, pneumococcal and *Haemophilus influenza* b vaccines: regular vaccination in infancy according to recommended immunization schedules, PLUS:
  - Meningococcal vaccination:
    - Meningococcal-C-Conjugate at age  $\geq 2$  yr + Quadrivalent Men-P-ACYW at least 2 wk later
    - Booster of Men-P-ACYW q2-5 yr
  - Pneumococcal vaccination:
    - Pneumococcal polysaccharide vaccine (Pneu-P-23) at age  $\geq 2$  yr
    - Single booster of Pneu-P-23 at age  $\geq 3$  yr
  - *Haemophilus influenzae* type b vaccination:
    - Consider single booster at age  $> 5$  yr



According to the CDC, the weight of currently available scientific evidence does not support the hypothesis that MMR vaccine causes either autism or IBD. The landmark paper linking autism to the MMR vaccine (*Lancet* 1998;351:637-641) was retracted due to false claims in the article (*Lancet* 2010;375:445).

**Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis**  
*NEJM* 2006;354:11-22

**Study:** Randomized, double-blind, phase 3 trial. Patients: 63,225 healthy infants from Latin America and Finland.

**Intervention:** Two oral doses of HRV vaccine vs. placebo at 2 and 4 mo of age.

**Outcome:** Episodes of gastroenteritis and severity  
**Results:** The vaccine is 85% efficacious against severe rotavirus gastroenteritis and hospitalizations associated with gastroenteritis and 100% efficacious against more severe gastroenteritis.

## Vaccine Administration

- injection site:
  - infants (<12 mo): anterolateral thigh
  - children: deltoid
- timing of injection:
  - DTaP+IPV+Hib given in single injection
  - varicella and MMR vaccines given at either the same visit or separated by  $>4$  wk (MMRV at 4-6 yr)
  - hepatitis B vaccine given in 3 doses of 0.5 mL (0, 1, 6 mo) either at school in grade 7 (2 adult doses of 1 mL one month apart for teens) (Ontario) or at birth if at increased risk (i.e. endemic country, mother or household contact HBsAg positive)
  - HPV-4 vaccine given in 3 doses (0, 2, 6 mo) to grade 8 females in Ontario schools

## Growth and Development

**Growth**

- growth is not linear:
  - most rapid growth during first two years and at puberty
  - tissues grow at different times
    - ♦ first two years = CNS; mid-childhood = lymphoid tissue; puberty = gonads
- measurement of growth:
  - premature infants (<37 wk) use corrected gestational age until age 2 yr
  - body proportion = upper / lower segment ratio (use symphysis pubis as midpoint)
    - ♦ newborn = 1.7, adult male = 0.97, adult female = 1.0



## Average Growth Parameters

**Table 3. Parameter of Average Growth**

	Normal	Growth	Comments
<b>Birth Weight</b>	3.25 kg (7 lbs)	Gain 20-30 g/d (term neonate) 2 x birth wt by 4-5 mo 3 x birth wt by 1 yr 4 x birth wt by 2 yr	Weight loss (up to 10% of birth wt) in first 7 d of life is normal Neonate should regain birth weight by ~10-14 d of age
<b>Length/Height</b>	50 cm (20 in)	25 cm in 1st yr 12 cm in 2nd yr 8 cm in 3rd yr then 4-7 cm/yr until puberty 1/2 adult height at 2 yr	Measure supine length until 2 yr of age, then measure standing height
<b>Head Circumference</b>	35 cm (14 in)	2 cm/mo for 1st 3 mo 1 cm/mo at 3-6 mo 0.5 cm/mo at 6-12 mo	Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference

## Reflexes

**Table 4. Reflexes**

Reflex	Maneuver to Elicit Reflex	Appropriate Reflex Response
Moro	Infant placed semi-upright, head supported by examiner's hand, sudden withdrawal of supported head with immediate resupport	Abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms
Galant	Infant held in ventral suspension and one side of back is stroked along paravertebral line	Pelvis will move in the direction of stimulated side
Grasp	Placement of examiner's finger in infant's palm	Flexion of infant's fingers
ATNR	Turn infant's head to one side	"Fencing" posture (extension of ipsilateral leg and arm and flexion of contralateral leg)
Placing	Dorsal surface of infant's foot placed touching edge of table	Flexion followed by extension of ipsilateral limb up onto table (resembles primitive walking)
Rooting	Tactile stimulus near mouth	Infant pursues stimulus with face
Parachute	Tilt infant to side while in sitting position	Ipsilateral arm extension, present by 6-8 mo

ATNR = asymmetric tonic neck reflex

## Developmental Milestones

**Table 5. Developmental Milestones**

Age*	Gross Motor	Fine Motor	Speech and Language	Adaptive and Social Skills
<b>1 month</b>	Turns head side to side when supine	Hands fisted, thumb in fist	Cries, startles to loud noises	Calms when comforted
<b>2 months</b>	Briefly raises head when prone, holds head erect when upright	Pulls at clothes	Variety of sounds (e.g. coos, gurgles)	Smiles responsively, recognizes and calms down to familiar voice, follows movement with eyes
<b>4 months</b>	Lifts head and chest when prone, holds head steady when supported sitting, rolls prone to supine	Briefly holds object when placed in hand, reaches for midline objects	Turns head towards sounds	Laughs responsively, follows moving toy or person with eyes, responds to people with excitement (e.g. leg movement)
<b>6 months</b>	Tripod sit, pivots in prone position	Ulnar grasp, transfers objects from hand to hand, brings objects to mouth	Babbles	Stranger anxiety, beginning of object permanence
<b>9 months</b>	Sits well without support, crawls, pulls to stand, stands with support	Early pincer grasp with straight wrist	"Mama, dada" – appropriate, imitates 1 word, responds to "no" regardless of tone	Plays games (e.g. peek-a-boo), reaches to be picked up
<b>12 months</b>	Gets into sitting position without help, stands without support, walks while holding on	Neat pincer grasp, releases ball with throw	2 words, follows 1-step command, uses facial expression, sounds, actions to make needs known	Responds to own name, separation anxiety begins

\*Use corrected gestational age until 2 yr



### Scoliosis Screening

Despite mass school screening implemented in parts of the USA and Canada in the 1970s-90s, the Canadian (1994) and American (2004) Task Forces on Preventive Health Care do NOT currently recommend routine screening using the Forward Bend Test (FBT). Cohort studies indicate that the forward bend test has poor sensitivity for identifying pathological curves. Furthermore, there is no evidence to suggest that screening and increased bracing lead to better outcomes.



### Abnormal Reflex Response

- Absence may suggest CNS abnormality
- Persistence after 4-6 mo may indicate abnormality (e.g. cerebral palsy)
- Asymmetry suggests focal motor lesions (e.g. brachial plexus injury)
- Upgoing plantar reflex (Babinski's sign) normal in infants up to age 2 yr



### Pediatric Developmental Milestones

- 1 yr: single words
- 2 yr: 2-word sentences; understands 2 step commands
- 3 yr: 3-word combinations; rides tricycle
- 4 yr: counts 4 objects

**Table 5. Developmental Milestones** (continued)

Age*	Gross Motor	Fine Motor	Speech and Language	Adaptive and Social Skills
<b>15 months</b>	Walks without support, crawls up stairs/steps	Picks up and eats finger foods, scribbles, stacks 2 blocks	Says 4-5 words, points to needs/wants	Looks to see how others react (e.g. after falling)
<b>18 months</b>	Runs, walks forward pulling toys or carrying objects	Tower of 3 cubes, scribbling, eats with spoon	10 words, follows simple commands	Show affection towards others, points to show interest in something
<b>24 months</b>	Climbs up 2 feet per step, runs, kicks ball, walks up and down steps	Tower of 6 cubes, undresses	2-3 word phrases, uses "I, me, you", 50% intelligible, understands 2-step commands	Parallel play, helps to dress
<b>3 years</b>	Tricycle, climbs up 1 foot per step, down 2 feet per step, stands on one foot briefly	Copies a circle, turns pages one at a time, puts on shoes, dress/undress fully except buttons	Combines 3 or more words into sentence, recognize colors, prepositions, plurals, counts to 10, 75% intelligible	Knows sex, age, shares some of the time, plays make-believe games
<b>4 years</b>	Hops on 1 foot, down 1 foot per step	Copies a cross, uses scissors, buttons clothes	Speech intelligible, uses past tense, 100% intelligible, understands 3-part directions	Cooperative play, fully toilet-trained by day, tries to comfort someone who is upset
<b>5 years</b>	Skips, rides bicycle	Copies a triangle and square, prints name, ties shoelaces	Fluent speech, future tense, alphabet, retells sequence of a story	Cooperates with adult requests most of the time, separates easily from caregiver

\*Use corrected gestational age until 2 yr

**Developmental Red Flags**

- Gross motor: not walking at 18 mo
- Fine motor: handedness at <10 mo
- Speech: <3 words at 18 mo
- Social: not smiling at 3 mo; not pointing at 15-18 mo

## Nutrition

### Dietary Requirement

Weight	<10 kg	10-20 kg	>20 kg
kcal	100 kcal/kg/d	1000 cal + 50 kcal/kg/d for each kg >10	1500 cal + 20 kcal/kg/d for each kg >20

### Dietary Recommendations

- 0 to 6 months: breast milk or formula
  - exclusive breast milk during first 6 mo recommended over formula unless contraindicated
  - breastfed infants require supplements: vitamin K (all babies get at birth, breastfed or not), vitamin D (400-800 IU/d), fluoride (after 6 mo if not sufficient in water), iron (6-12 mo, only if not receiving fortified cereals/meat/meat alternatives)
- >6 months: solid food introduction – do not delay beyond 9 mo
  - 2 to 3 new foods per week with a few days in between each food to allow time for adverse reaction identification
  - suggested order of introduction:
    - ♦ meat, meat alternatives, and iron enriched cereal (rice cereal is least allergenic)
    - ♦ pureed vegetables
    - ♦ fruit
- 9 to 12 months: finger foods and switch to homogenized (3%) milk
  - foods to avoid:
    - ♦ honey until past 12 mo (risk of botulism)
    - ♦ added sugar, salt
    - ♦ excessive milk (i.e. no more than 16 oz/d after a yr)
    - ♦ juice (not nutritious, too much sugar)
    - ♦ anything that is a choking hazard (chunks, round foods like grapes)

### Breastfeeding

- content of breast milk:
  - colostrum (first few days): clear, rich in nutrient (i.e. high protein, low fat), immunoglobulin
  - mature milk: 70:30 whey:casein ratio, fat from dietary butterfat, carbohydrate from lactose
- advantages:
  - easily digested, low renal solute load
  - immunologic
    - ♦ contains IgA, macrophages, active lymphocytes, lysozymes, lactoferrin (which inhibits *E. coli* growth in intestine)
    - ♦ lower pH promotes growth of lactobacillus in GI tract
  - parent-child bonding
  - economical, convenient

- contraindicated if mother:
  - is receiving chemotherapy or radioactive compounds
  - has HIV/AIDS, active untreated TB, herpes in breast region
  - is using >0.5 g/kg/d alcohol or illicit drugs
  - is taking medications known to cross to breast milk
  - oral contraceptive pills *not* a contraindication to breastfeeding (estrogen may decrease lactation, but is not dangerous to infant)
  - MotherRisk – valuable research and counselling on reproductive risk or safety of drugs, chemicals, and maternal disease
- complications in infant:
  - breastfeeding jaundice (first 1-2 wk): due to lack of milk production and subsequent dehydration (see *Jaundice*, P73), likely mechanical problem
  - breast milk jaundice (0.5% of newborns, persists up to 4-6 mo): rare, not fully understood, thought to be due to substances in breast milk that inhibit conjugation of bilirubin or increase enterohepatic circulation of bilirubin, likely a biochemical problem. Check bilirubin to rule out conjugated hyperbilirubinemia.
    - ♦ baby presents healthy and thriving, and jaundice resolves
  - poor weight gain: consider dehydration or failure to thrive
  - oral candidiasis (thrush): check baby's mouth for white cheesy material that does not scrape off; treat baby with antifungal such as nystatin (Mycostatin®) (treat mother topically to prevent transmission). Can occur in breast or bottle-fed infants.

**Table 6. Formula Compared to Breast Milk**

Type of Nutrition	Indications	Content (as compared to breast milk)
<b>Cow's milk based</b> (Enfamil®, Similac®)	Prematurity Transition into breastfeed Contraindication to breastfeed	Lower whey:casein ratio Plant fats instead of dietary butterfat
<b>Fortified formula</b>	Low birth weight Prematurity	Higher calories and vitamins A, C, D, K May only be used in hospital due to risk of fat-soluble vitamin toxicity
<b>Soy protein</b> (Isomil®, Prosobee®)	Galactosemia Lactose intolerance (note: true lactose intolerance rare in children under age 5)	Corn syrup solids or sucrose in place of lactose
<b>Partially hydrolyzed proteins</b> (Good Start®)	Delayed gastric emptying Risk of cow's milk allergy	Protein is 100% whey with no casein
<b>Protein hydrolysate</b> (Nutramigen®, Alimentum®, Pregestimil®, Portagen®)	Malabsorption Food allergy	Protein is 100% casein with no whey Corn syrup solids, sucrose or tapioca starch instead of lactose Expensive
<b>Amino acid</b> (Neocate®)	Food allergy Short gut	Free amino acids (no protein) Corn syrup solids instead of lactose Very expensive
<b>Metabolic</b>	Inborn errors of metabolism	Various different compositions for children with galactosemia, propionic acidemia, etc.

**Medications that Cross into Breast Milk:**

- antimetabolites
- bromocriptine
- chloramphenicol
- high dose diazepam
- ergots
- gold
- metronidazole
- tetracycline
- lithium
- cyclophosphamide

**Signs of Inadequate Intake:**

- <6 wet diapers/d after first wk
- <7 feeds/d
- Rule of thumb: ~1 stool/d of age for first wk
- Sleepy or lethargic, sleeping throughout the night <6 wk
- Weight loss >10% of birth weight
- Jaundice

**Nutrition for Healthy Term Infants, Birth to Six Months: An Overview**

*Paediatric Child Health* 2013;18:206-207

**Study:** Guidelines by the Canadian Pediatric Society (CPS).

**Patients:** Healthy term infants.

**Recommendations:** The Nutrition and Gastroenterology Committee of the Canadian Paediatric Society recommend exclusive breastfeeding for the first 6 mo of life with a daily vitamin D supplement of 10 µg (400 IU) for healthy, term, breastfed infants. When transitioning to solid foods, the committee recommends meat, meat alternatives and iron-fortified cereal.



There is no evidence that restriction of highly allergenic foods is beneficial in the first year of life. There is also no evidence that dietary restrictions during pregnancy or breastfeeding are protective to the child. May consider restricting nuts for risk of severe reactions.

## Injury Prevention Counselling

- injuries are the leading cause of death in children >1 yr of age
- main causes: motor vehicle crashes, burns, drowning, falls, choking, infanticide

**Table 7. Injury Prevention Counselling**

0-6 months	6-12 months	1-2 years	2-5 years
Do not leave alone on bed, on change table or in tub	Install stair barriers	Never leave unattended	Bicycle helmet
Keep crib rails up	Discourage use of walkers	Keep pot handles turned to back of stove	Never leave unsupervised at home, driveway or pool
Check water temperature before bathing	Avoid play areas with sharp-edged tables and corners	Caution with whole grapes, nuts, raw carrots, hotdogs, etc. due to choking hazard	Teach bike safety, stranger safety, and street safety
Do not hold hot liquid and infant at the same time	Cover electrical outlets	No running while eating	Swimming lessons (>4 yr), sunscreen (from 6 mo), toddler seats in the car, fences around pools, dentist by age 3
Check milk temperature before feeding	Unplug appliances when not in use		
Appropriate car seats are required before leaving hospital	Keep small objects, plastic bags, cleaning products, and medications out of reach		
	Supervise during feeding		

## Common Complaints

### Breath Holding Spells

- epidemiology: 0.1-5% of healthy children 6 mo-4 yr of age, usually start during first year of life
- etiology: child is provoked (usually by anger, injury, or fear) → holds breath and becomes silent → spontaneously resolves or loses consciousness
- types:
  - cyanotic (more common), usually associated with anger/frustration
  - pallid, usually associated with pain/surprise
- management:
  - usually resolves spontaneously and rarely progresses to seizure
  - help child control response to frustration and avoid drawing attention to spell

### Circumcision

- elective procedure
  - not covered by OHIP in Ontario, but recent evidence shows health benefits outweigh risks and justify access to procedure
  - often for religious or culture reasons
- benefits: prevention of phimosis and slightly reduced incidence of UTI, balanitis, cancer of the penis
- complications (<1%): local infection, bleeding, urethral injury
- contraindications: presence of genital abnormalities (e.g. hypospadias) or known bleeding disorder



#### Circumcision

*Pediatrics* 2012;130:e756-e785

**Study:** Guidelines by the American Academy of Pediatrics (AAP).

**Recommendations:** The American Academy of Pediatrics radically changed their position on male circumcision in 2012. The report from the AAP now states that the preventative health benefits outweigh the risks of the procedure and that the procedure is well-tolerated with adequate pain management and sterility. Stated benefits include the prevention of urinary tract infection, penile cancer, transmission of some sexually transmitted infections, including HIV. There is believed to be no effect on penile sexual function, sensitivity or sexual satisfaction. Acute complications are rare and more common if the procedure is done by an untrained provider.

**Note:** The Canadian Pediatric Society (CPS) has not yet updated their position on male circumcision since 1996, which stated that the CPS is opposed to routine circumcision. A new statement is expected soon.

### Crying/Fussing Child

- history:
  - description of baseline feeding, sleeping, crying patterns
  - infectious symptoms: fever, tachypnea, rhinorrhea, ill contacts
  - feeding intolerance: gastroesophageal reflux with esophagitis, nausea, vomiting, diarrhea, constipation
  - trauma
  - recent immunizations (vaccine reaction) or medications (drug reactions), including maternal drugs taken during pregnancy (neonatal withdrawal syndrome) and drugs that may be transferred via breast milk
  - inconsistent history, pattern of numerous emergency department visits, high-risk social situations all raise concern of abuse

**Table 8. Physical Examination and Differential Diagnosis**

Organ System	Examination Findings	Possible Diagnosis
<b>HEENT</b>	Bulging fontanelle Blepharospasm, tearing Retinal hemorrhage Oropharyngeal infections	Meningitis, shaken baby syndrome, hydrocephalus Corneal abrasion, glaucoma Shaken baby syndrome Thrush, gingivostomatitis, herpangina, otitis media
<b>Neurological</b>	Irritability or lethargy	Meningitis, shaken baby syndrome
<b>Cardiovascular</b>	Poor perfusion  Tachycardia	Sepsis, anomalous coronary artery, meningitis, myocarditis, congestive heart failure (CHF) Supraventricular tachycardia
<b>Respiratory</b>	Tachypnea Grunting	Pneumonia, CHF Respiratory disease, response to pain
<b>Abdominal</b>	Mass, empty RLQ	Intussusception
<b>Genitourinary</b>	Scrotal swelling Penile/clitoral swelling	Incarcerated hernia, testicular torsion Hair tourniquet
<b>Rectal</b>	Anal fissure Hemoccult positive stool	Constipation or diarrhea Intussusception, necrotizing enterocolitis, volvulus
<b>Musculoskeletal</b>	Point tenderness or decreased movement	Fracture, syphilis, osteomyelitis, toe/finger hair tourniquet

## Dentition and Caries

### Dentition

- primary dentition (20 teeth)
  - first tooth at 5-9 mo (lower incisor), then 1 per month
  - 6-8 central teeth by 1 yr
  - assessment by dentist 6 mo after eruption of first tooth and certainly by 1 yr of age (Grade B recommendation)
- secondary dentition (32 teeth)
  - first adult tooth is 1st molar at 6 yr, then lower incisors

### Caries

- milk caries: decay of superior front teeth and back molars in first 4 yr of life
- cause: often due to prolonged feeding (e.g. put to bed with bottle, prolonged breastfeeding)
- prevention:
  - no bottle at bedtime, clean teeth after last feed
  - minimize juice and sweetened pacifier
  - clean teeth with soft damp cloth or toothbrush and water
  - water fluoridation

## Enuresis

### Definition

- involuntary urinary incontinence by day and/or night in child >5 yr

### General Approach

- should be evaluated if dysuria, change in colour, odour, stream, secondary or diurnal, change in gait, stool incontinence

### Primary Nocturnal Enuresis

- definition: wet only at night during sleep, bladder control has never been attained
- epidemiology: boys > girls; 10% of 6 yr olds, 3% of 12 yr olds, 1% of 18 yr olds
- etiology: developmental disorder or maturational lag in bladder control while asleep
- management:
  - time and reassurance (~20% resolve spontaneously each yr)
  - behaviour modification (limiting fluids, voiding prior to sleep), bladder retention exercises, scheduled toileting has limited effectiveness
  - conditioning: "wet" alarm wakes child upon voiding (70% success rate)
  - medications (considered second line therapy, may be used for sleepovers/camp): DDAVP oral tablets (high relapse rate, costly), imipramine (Tofranil\*) (rarely used, lethal if overdose, cholinergic side effects)



Treatment for primary nocturnal enuresis should not be considered until 7 yr of age due to high rate of spontaneous cure.

### Secondary Enuresis

- definition: develops after child has sustained period of bladder control (>6 mo)
- etiology: inorganic regression due to stress or anxiety (e.g. birth of sibling, significant loss, family discord), focused on other activities, secondary to organic disease (UTI, DM, DI, neurogenic bladder, cerebral palsy (CP), sickle cell disease, seizures, pinworms)
- management: treat underlying cause

### Diurnal Enuresis

- definition: daytime wetting (60-80% also wet at night)
- etiology: micturition deferral (holding urine until last minute) due to psychosocial stressor (e.g. shy), structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders
- management: treat underlying cause, behavioural (scheduled toileting, double voiding, good bowel program), pharmacotherapy

## Encopresis

- definition: fecal incontinence in a child >4 yr old, at least once per month for 3 months
- prevalence: 1-1.5% of school-aged children (rare in adolescence); M:F = 6:1 in school-aged children
- causes: chronic constipation (retentive encopresis), Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, anorectal malformations

## Retentive Encopresis

- definition
  - child holds bowel movement, develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
- etiology
  - physical: painful stooling often secondary to constipation
  - emotional: disturbed parent-child relationship, coercive toilet training, social stressors
- clinical presentation
  - history
    - ♦ crosses legs or stands on toes to resist urge to defecate
    - ♦ distressed by symptoms, soiling of clothes
    - ♦ toilet training coercive or lacking in motivation
    - ♦ may show oppositional behavior
    - ♦ abdominal pain
  - physical exam
    - ♦ digital rectal exam: large fecal mass in rectal vault
    - ♦ anal fissures (result from passage of hard stools)
    - ♦ palpable stool in LLQ
- management
  - complete clean-out of bowel: PEG 3350 given orally is most effective, enemas and suppositories may be second line therapies, but these are invasive and often less effective
  - maintenance of regular bowel movements (see *Pediatric Gastroenterology, Constipation Treatment*, P38)
  - assessment and guidance regarding psychosocial stressors
  - behavioural modification
- complications: recurrence, toxic megacolon (requires >3-12 mo to treat), bowel perforation

## Failure to Thrive



- definition
  - weight <3rd percentile, or falls across two major percentile curves, or <80% of expected weight for height and age
  - inadequate caloric intake most common factor in poor weight gain
  - may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
  - factors affecting physical growth: genetics, intrauterine factors, internal time clock, nutrition, endocrine hormones, chronic infections/diseases, psychosocial factors
- clinical presentation
  - history
    - ♦ nutritional intake
    - ♦ current symptoms
    - ♦ past illnesses
    - ♦ family history: growth, puberty, parental height and weight including mid-parental height
    - ♦ psychosocial history
- physical exam
  - ♦ growth parameters, plotted: height (Ht), weight (Wt), head circumference (HC), arm span
  - ♦ vital signs
  - ♦ complete head to toe exam
  - ♦ dysmorphic features or evidence of chronic disease
  - ♦ upper to lower segment ratio
  - ♦ sexual maturity staging
  - ♦ signs of abuse or neglect
- investigations (as indicated by clinical presentation)
  - CBC, blood smear, electrolytes, T4, TSH, GH, IGF-1
  - bone age x-ray
  - chromosomes/karyotype
  - chronic illness: chest (CXR, sweat Cl<sup>-</sup>), cardiac (CXR, ECG, ECHO), GI (celiac screen, inflammatory markers, malabsorption), renal (urinalysis), liver (enzymes, albumin)



### Energy Requirements

- 0-10 kg: 100 kcal/kg/d
- 1-20 kg: 1,000 kcal + 50 kcal/kg/d for each kg >10
- >20 kg: 1,500 kcal + 20 kcal/kg/d for each kg >20



### Calculating Upper to Lower (U/L) Segment Ratio

- Upper segment: Top of head to pubic symphysis
- Lower segment: Pubic symphysis to floor
- U/L: upper segment/lower segment



### Upper to Lower (U/L) Segment Ratio

- **Increased** in achondroplasia, short limb syndromes, hypothyroid, storage diseases
- **Decreased** in Marfan's, Klinefelter's, Kallman's syndromes, and testosterone deficiency



### Mid-Parental Height (MPH)

- Boys target height = (father ht + mother ht + 13)/2
- Girls target height = (father ht + mother ht - 13)/2

**Table 9. Failure to Thrive Patterns**

Healthy	Medical Illness	Non-Organic
<b>Weight</b> and <b>height</b> proportionally small Familial (BA = CA) Constitutional Growth Delay (BA < CA)	<b>Weight</b> and <b>height</b> proportionally small Syndrome Chromosomal  <b>Weight</b> falls more than height (FTT) Chronic illness Lack of intake  <b>Height</b> falls more than weight (short stature) Endocrine	<b>Weight</b> falls more than height (FTT) Multifactorial

BA=bone age; CA=chronological age



**Organic FTT (10%)**

- inadequate intake
  - non-organic
  - vomiting, oromotor dysfunction, anorexia
- excessive consumption
  - CHD, CF, hyperthyroidism
- abnormal utilization
  - inborn errors of metabolism
- excessive output
  - IBD, celiac, malabsorption
- management: treat specific cause

**Non-Organic FTT (90%)**

- most common cause of FTT
- results from complex factors in parent-child relationship
  - dietary intake, knowledge about feeding
  - feeding environment
  - parent-child interaction, attachment
  - child behaviours, hunger/satiety cues
  - social factors – stress, poverty
- management
  - most as outpatient using multidisciplinary approach: primary care physician, dietitian, psychologist, social work, child protection services
  - medical: oromotor problems, iron-deficient anemia, gastroesophageal reflux
  - nutritional: educate about age-appropriate foods, calorie boosting, mealtime schedules and environment to reach goal of 90-110% IBW, correct nutritional deficiencies, and promote catch-up growth/development
  - behavioural: positive reinforcement, mealtime environment

**Energy Requirements**

- see *Nutrition*, P6

**Clinical Signs of FTT****SMALL KID**

Subcutaneous fat loss

Muscle atrophy

Alopecia

Lethargy

Lagging behind normal

Kwashiorkor

Infection (recurrent)

Dermatitis

**Infantile Colic**

- definition: unexplained paroxysms of irritability and crying for >3 h/d, >3 d/wk for >3 wk in an otherwise healthy, well-fed baby (rule of 3s)
- epidemiology: 10% of infants; usual onset 10 d to 3 mo of age with peak at 6-8 wk
- etiology: lag in development of normal peristaltic movement in gastrointestinal tract; other theories suggest a lack of self-soothing mechanisms or extreme of normal
- management:
  - parental relief, rest and reassurance
  - hold baby, soother, car ride, music, vacuum, check diaper
  - medications (Ovol® drops, gripe water) have no proven benefit, some evidence for probiotics
  - if breastfeeding, elimination of cow's milk protein from mother's diet (effective in very small percentage of cases)
  - try casein hydrosylates formula (Nutramigen®)
  - time – all resolve, most in the first 2-3 mo of life

**Obesity**

- definition: BMI >95th percentile for age and height
- risk factors: genetic predisposition (e.g. both parents obese – 80% chance of obese child)
- etiology: organic causes are rare (<5%): Prader-Willi, Carpenter, Turner, Cushing syndromes, hypothyroidism
- complications: association with hypertension, dyslipidemia, slipped capital femoral epiphysis, type 2 diabetes, asthma, obstructive sleep apnea, gynecomastia, polycystic ovarian disease, early menarche, irregular menses, psychological trauma (e.g. teasing, decreased self-esteem, unhealthy coping mechanisms, depression)
- childhood obesity is not reliable predictor of adult obesity unless >180% ideal body weight, adolescent obesity good predictor of adult obesity
- management:
  - encouragement and reassurance; engagement of entire family
  - diet: qualitative changes (do not encourage weight loss, but allow for linear growth to catch up with weight), special diets used by adults are not encouraged
  - very low calorie diets for preadolescents are not recommended
  - behaviour modification: increase activity, change eating habits/meal patterns
  - education: multidisciplinary approach, dietitian, counselling
  - surgery and pharmacotherapy are not frequently used in children
  - increase activity, reduce screen time

**Geographic and Demographic Variation in the Prevalence of Overweight Canadian Children**  
*Obesity Research 2003;11:668-673***Purpose:** To determine geographic and demographic variation in the prevalence of overweight Canadian children.**Study:** Assessment of trends in BMI using data from the 1981 Canadian Fitness Survey and the 1996 National Longitudinal Survey of Children and Youth.**Main Outcomes:** The prevalence of overweight and obese children age 7-13 yr, secular trends from 1981 to 1996 by province, and provincial variation after adjusting for socioeconomic and demographic characteristics.**Results:** In 1996, 33% of boys and 26% of girls were classified as overweight, and 10% of boys and 9% of girls were classified as obese. The odds ratio associated with the 1981 to 1996 change in the prevalence of overweight children was 3.24 (95% CI, 2.83-3.70) for Canada as a whole. There are clear regional differences, with those in Atlantic Canada more likely to be overweight and Prairie children less likely. These differences were not sufficiently accounted for by differences in socioeconomic circumstances.**Conclusions:** The prevalence of childhood obesity is increasing in all areas of Canada, although more so in Atlantic Canada.

## Poison Prevention

- keep all types of medicines, vitamins, and chemicals locked up in a secure container
- potentially dangerous: drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- keep alcoholic beverages out of reach: 3 oz hard liquor can kill a 2-yr-old
- always read labels before administering medicine to ensure correct drug and dose

## Rashes

**Table 10. Common Pediatric Rashes**

Type of Rash	Differential	Appearance	Management
<b>Diaper Dermatitis</b>			
	Irritant contact dermatitis	Shiny, red macules/patches, no flexural involvement	Eliminate direct skin contact with urine and feces, allow periods of rest without a diaper, frequent diaper changes, topical barriers (petrolatum, zinc oxide or paste), short-term low-potency topical corticosteroids (severe cases)
	Seborrheic dermatitis	Yellow, greasy macules/plaques on erythema, scales	Short-term topical low-potency corticosteroid
	Candidal dermatitis	Erythematous macerated papules/plaques, satellite lesions	Antifungal agents
<b>Other Dermatitis</b>			
	Atopic dermatitis	Erythematous papules/plaques, oozing, excoriation, lichenification, classic areas of involvement	Eliminate exacerbating factors, maintain skin hydration, corticosteroids, topical calcineurin inhibitor
	Nummular dermatitis	Annular erythematous plaques, oozing, crusting	Avoid irritant if identified, potent topical steroid in emollient base, short-term systemic steroids $\pm$ antibiotics (severe)
	Allergic contact dermatitis	Red papules/plaques/vesicles/bullae, only in area of allergen	Mild: soothing lotion (i.e. calamine lotion) Moderate: topical moderate/strong potency Severe: systemic corticosteroids and antihistamine
	Irritant contact dermatitis	Morphology depends on irritant	Avoid skin contact
	Dyshidrotic dermatitis	Papulovesicular, cracking/fissuring, hands and feet ("Tapioca pudding")	Mild/Moderate: medium/potent topical corticosteroids Severe: systemic corticosteroids, local PUVA or UVA treatments
	Seborrheic dermatitis	See above, sebaceous areas such as nasolabial folds and scalp	
<b>Infectious</b>			
	Scabies	Polymorphic (red excoriated papules/nodules, burrows), in web spaces/folds, very pruritic	Permethrin (Nix) 5% cream for patient and family (2 applications, 1 wk apart)
	Impetigo	Honey-coloured crusts or superficial bullae	Oral antibiotics (e.g. cephalexin/erythromycin) Topical if mild: fucidic acid or mupirocin cream
	Tinea corporis	Round erythematous plaques, central clearing and scaly border	Topical anti-fungal for skin, systemic anti-fungals for nails/head
<b>Pediatric Exanthems</b> (see <i>Infectious Pediatric Exanthems</i> , P58, <a href="#">Dermatology</a> , D40)			
<b>Drug Reactions</b> (see <a href="#">Dermatology</a> , D22)			
<b>Acne</b> (see <a href="#">Dermatology</a> , D11)			



## Sleep Disturbances

### Types of Sleep Disturbances

- insufficient sleep quantity
  - difficulty falling asleep (e.g. Limit Setting Sleep Disorder)
    - ♦ preschool and older children
    - ♦ bedtime resistance
    - ♦ due to caregiver's inability to set consistent bedtime rules and routines
    - ♦ often exacerbated by child's oppositional behaviours

- poor sleep quality
  - frequent arousals (e.g. sleep-onset association disorder)
    - ♦ infants and toddlers
    - ♦ child learns to fall asleep only under certain conditions or associations (with parent, held, rocked or fed, with light on, in front of television), and child loses ability to self-soothe
    - ♦ during the normal brief arousal periods of sleep (q90-120 min), child cannot fall back asleep because same conditions are not present
  - obstructive sleep apnea
    - ♦ epidemiology: 1-5% of preschool aged children, more common in black children
    - ♦ definition: partial or intermittent complete airway obstruction during sleep causing disrupted ventilation and sleep pattern
    - ♦ features: snoring/gasping/noisy breathing during sleep and irritable/tired/hyperactive during the day
    - ♦ sequelae: cardiovascular (hypertension/LV remodeling due to sympathetic activation), growth, cognitive, and behavioural deficits
    - ♦ risk factors: adenotonsillar hypertrophy, obesity
    - ♦ management: watchful waiting, weight reduction, airway pressure devices, or surgery depending on the cause
    - ♦ adenotonsillectomy does not improve executive function or attention but reduces symptoms and improves behaviour, quality of life, and polysomnographic findings
- parasomnias
  - episodic nocturnal behaviours
  - often involves cognitive disorientation and autonomic/skeletal muscle disturbance
  - e.g. sleep walking, sleep terrors, nightmares

### Management of Sleep Disturbances

- set strict bedtimes and “wind-down” routines
- do not send child to bed hungry
- positive reinforcement for limit setting sleep disorder
- always sleep in bed, in a dark, quiet, and comfortable room, without associations
- do not use bedroom for timeouts
- systematic ignoring and gradual extinction for sleep onset association disorder

### Nightmares

- epidemiology: common in boys, 4-7 yr old
- associated with REM sleep (anytime during night)
- features: upon awakening, child is alert and clearly recalls frightening dream
  - ± associated with daytime stress/anxiety
- management: reassurance

### Night Terrors

- epidemiology: 15% of children have occasional episodes
- abrupt sitting up, eyes open, screaming
- clinical features: occurs in early hours of sleep, stage 4 of sleep; signs of panic and autonomic arousal, no memory of event, inconsolable, stress/anxiety can aggravate them
- course: remits spontaneously at puberty
- management: reassurance for parents, ensure child is safe (e.g. if sleepwalks)



#### Daily Sleep Requirement

- <6 mo 16 h
- 6 mo 14.5 h
- 12 mo 13.5 h
- 2 yr 13 h
- 4 yr 11.5 h
- 6 yr 9.5 h
- 12 yr 8.5 h
- 18 yr 8 h

#### Nap Patterns

- 2/d at 1 yr
- 1/d at 2 yr: 2-3 h
- 0.5/d at 5 yr: 1.7 h

## Toilet Training

- 90% of children attain bladder control before bowel control
- generally females train earlier than males
- 25% by 2 yr old (in North America), 98% by 3 yr old have daytime bladder control
- signs of toilet readiness:
  - ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several hours (large enough bladder), can recognize need to go, able to remove clothing

## Sudden Infant Death Syndrome (SIDS)



### Definition

- sudden and unexpected death of an infant <12 mo of age in which the cause of death cannot be found by history, examination, or a thorough postmortem and death scene investigation

### Epidemiology

- 0.5/1000 (leading cause of death between 1-12 mo of age); M:F = 3:2
- more common in children placed in prone position
- in full term infants, peak incidence is 2-4 mo, 95% of cases occur by 6 mo
- increase in deaths during peak respiratory syncytial virus (RSV) season
- most deaths occur between midnight and 8 AM

**Risk Factors**

- prematurity, smoking in household, socially disadvantaged, higher incidence in aboriginals and African Americans
- risk of SIDS is increased 3-5x in siblings of infants who have died of SIDS

**Prevention**

- “Back to Sleep, Front to Play” (place infant on back when sleeping)
- allow supervised play time daily in prone position (“tummy time”)
- alarms, monitors not recommended – increase anxiety, do not prevent life-threatening events
- avoid overheating and overdressing
- appropriate infant bedding (firm mattress, avoid loose bedding and crib bumper pads)
- no smoking
- risks associated with bedsharing: sleeping on a sofa, sleeping with an infant after consumption of alcohol/street drugs, infant sleeping with someone other than primary caregiver
- pacifiers appear to have a protective effect; do not reinsert if falls out

**Apparent Life-Threatening Events (ALTEs)**

A group of conditions often marked by an episode of apnea, cyanosis, change in tone, or change in mental status occurring in a child, where an observer fears the child may be dying. There is no clear connection between most ALTEs and SIDS. Evaluating for a cause of the ALTE (e.g. infection, cardiac, neurologic) is guided by history, physical examination and period of observation.



## Child Abuse and Neglect

**Definition**

- an act of commission (physical, sexual, or psychological abuse) or omission (neglect) by a caregiver that harms a child

**Legal Duty to Report**

- upon reasonable grounds to suspect abuse and/or neglect, physicians are required by legislation to contact the Child Protective Services (CPS) to personally disclose all information relevant to the child safety concern
- duty to report overrides patient confidentiality; physician is protected against liability

**Ongoing Duty to Report**

- if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the CPS must be made

**Risk Factors**

- environmental factors: social isolation, poverty, domestic violence
- caregiver factors: personal history of abuse, psychiatric illness, substance abuse, single parent family, poor social and vocational skills, below average intelligence
- child factors: difficult temperament, disability, special needs (e.g. developmental delay), premature

## Physical Abuse

**History**

- history that is not compatible with physical findings, or history not reproducible
- delay in seeking medical attention that is unexplained by other factors

**Physical Exam**

- physical findings not explained by underlying medical condition
- growth parameters (weight, height, head circumference)
- recurrent or multiple injuries not explained by accidental injury or child's development level
- patterned skin injuries: belt buckle, hand prints, burns that do not match provided history
- injury location: bruises on areas with abundant soft-tissue cushioning, such as abdomen, buttocks, genitalia, fleshy part of cheek; bruises on ears; posterior rib/metaphyseal/scapular/vertebral/sternal fractures (more suspicious for non-accidental injuries); immersion burns (e.g. hot water)
- altered mental status: head injury, poisoning
- head trauma is the leading cause of death in child maltreatment [e.g. acceleration-deceleration forces (shaking), direct force application (blow or impact)]

**Investigations**

- document all injuries on a body diagram: type, location, size, shape, colour, pattern
  - photography of skin injuries is ideal (police or hospital photography preferred; do not use physician's personal camera)
- blood tests to rule out medical causes (e.g. thrombocytopenia or coagulopathy)
- screen for abdominal trauma (transaminases and amylase): if increased, abdo CT recommended
- skeletal survey in children <2 yr:
  - bone scan can be beneficial for assessing rib fractures (not helpful for skull or metaphyseal region due to active bone growth) – consider bone scan if equivocal findings on initial skeletal survey
  - dilated eye examination by pediatric ophthalmologist to rule out retinal hemorrhage
  - be aware of “red herrings” (e.g. Mongolian blue spots vs. bruises)
  - neuroimaging: CT and/or MRI



“If no bruising, no bruising.”

**Presentation of Neglect**

- Failure to thrive, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents, no stranger anxiety

## Sexual Abuse

### Epidemiology

- peak ages at 2-6 and 12-16 yr
- most perpetrators are male and known to child
  - in decreasing order: family member, non-relative known to victim, stranger

### History

- diagnosis usually depends on child disclosing to someone or forensic interview done by a trained individual
- psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of trust, low self-esteem, school failure, sexually aggressive behaviour, advanced sexual knowledge, sexual preoccupation or play

### Physical Exam

- recurrent UTIs, pregnancy, STIs, vaginitis, vaginal bleeding, pain, genital injury, enuresis

### Investigations

- depend on presentation, age, sex, and pubertal development of child
  - sexual assault examination kit within 24 h if prepubertal, within 72 h if pubertal
  - rule out STI, UTI, pregnancy (consider STI prophylaxis or emergency contraception)
  - rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)

## Neglect

### History

- from child and each caregiver separately (if possible)

### Physical exam

- head to toe (do not force), growth parameters, nutrition status
- dental care
- emotional state

### Investigations

- blood tests to rule out medical causes (e.g. thrombocytopenia or coagulopathy)

### Management of Physical Abuse, Child Abuse and Neglect

- report all suspicions to CPS; request emergency visit if imminent risk to child or any siblings in the home
- acute medical care: hospitalize for medical evaluation or treatment of injuries if indicated
- arrange consultation to social work and appropriate follow-up
- may need to discharge child directly to CPS or to responsible guardian under CPS supervision

## Adolescent Medicine

### Adolescent History (HEEADSSS)

- tailor your history according to the clinical context

**Home:** Who do you live with? What kind of place do you live in?

**Education/Employment:** What grade are you in? What are your favourite subjects? What was your average on your last report card?

**Eating:** Tell me about your meals/snacks in a typical day? Have you ever gone on a diet? (for *Eating Disorders* – see [Psychiatry](#), PS29)

**Activities:** What do you do after school? On the weekends? How much time do you spend on the computer/watching TV every day? Do you use Facebook?

**Drugs:** Which seems to be more popular at your school, alcohol or drugs? How often do you drink/smoke marijuana/take other drugs? Do you smoke cigarettes? When you drink, do you usually get drunk? Have you ever passed out or not been able to remember what happened while you were drinking? Has anything bad ever happened to you while you were drunk or stoned? (for *Substance Abuse* – see [Psychiatry](#), PS21)

**Sexuality:** Are you romantically interested in anyone? When you think about having sex with someone, do you think about girls, boys or both? Have you ever had sex with anyone? Whether the answer is yes or no, the next question is: What activities would you include in the term 'having sex'? What do you do to prevent getting a sexually transmitted infection/getting pregnant/getting someone pregnant? Has anyone ever given you money, drugs or other stuff in exchange for sex? (for *Sexually Transmitted Infections* – see [Gynecology](#), GY26)



### Adolescent Psychosocial Assessment

#### HEEADSSS

Home  
Education/Employment  
Eating  
Activities  
Drugs  
Sexuality  
Suicide and depression  
Safety



Rates of drug use in high school students who have used in the past year: alcohol (58.2%), cannabis (25.6%), tobacco (11.7%).



**Suicidality/Depression:** On a scale of 1 to 10, where 1 is so sad that you might kill yourself and 10 is the happiest you could be, where are you most days? Is there a difference between school days and the weekend? Have you ever thought seriously about suicide? Did you make a plan? (for *Depression/Suicide* – see [Psychiatry](#), PS9, PS4)

**Safety/Violence:** Do you ever get into a car with a driver who has been drinking? Do you always wear a seatbelt/bicycle helmet? Are you being bullied at school? Has anyone ever touched you in an unwanted way?

For *Normal and Abnormal Pubertal Development*, P31



Prevalence rates of depression: 1-2% in pre-pubertal children and 6-8% in adolescents.



Date rape comprises 80% of sexual assault in teenagers.

## Cardiology

### Congenital Heart Disease (CHD)

#### PRENATAL CIRCULATION

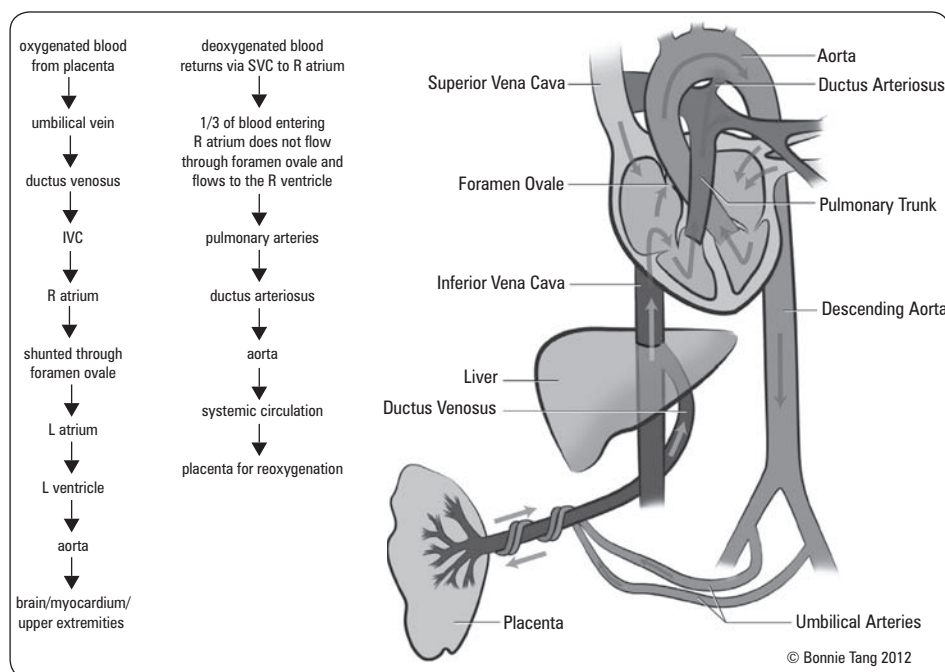


Figure 1. Prenatal circulation

#### Embryologic Development

- most critical period of fetal heart development is between 3-8 wk gestation
- single heart tube grows rapidly forcing it to bend back upon itself and assume the shape of a four chambered heart, insults at this time are most likely to lead to CHD

#### Before Birth

- fetal lungs are bypassed by flow through fetal shunts:
  - shunting deoxygenated blood
    - ♦ ductus arteriosus: connection between pulmonary artery and aorta
  - shunting oxygenated blood
    - ♦ foramen ovale: connection between R and L atria
    - ♦ ductus venosus: connecting between umbilical vein and IVC
- circulation (Figure 1)

#### At Birth

- with first breath, lungs open up and pulmonary resistance decreases allowing pulmonic blood flow
- separation of low resistance placenta → systemic circulation becomes a high resistance system → ductus venosus closure
- increased pulmonic flow → increased left atrial pressures → foramen ovale closure
- increased oxygen concentration in blood after first breath → decreased prostaglandins → ductus arteriosus closure
- closure of fetal shunts and changes in vascular resistance → infant circulation assumes normal adult flow



Fetal circulation is designed so that oxygenated blood is preferentially delivered to the brain and myocardium.



### Epidemiology

- 8/1000 live births have CHD, which may present as a heart murmur, heart failure, or cyanosis; ventricular septal defect is the most common lesion

### Investigations

- Echocardiogram, ECG, CXR

### CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE

- cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 3 g/dL
- acyanotic heart disease: (i.e. L to R shunt, obstruction occurring beyond lungs) blood passes through pulmonary circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis
- cyanotic heart disease: (i.e. R to L shunt) blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis



#### Characteristic Chest X-Ray Findings in Congenital Heart Disease

- Boot-shaped heart: tetralogy of Fallot, tricuspid atresia
- Egg-shaped heart: transposition of great arteries
- "Snowman" heart: total anomalous pulmonary venous return

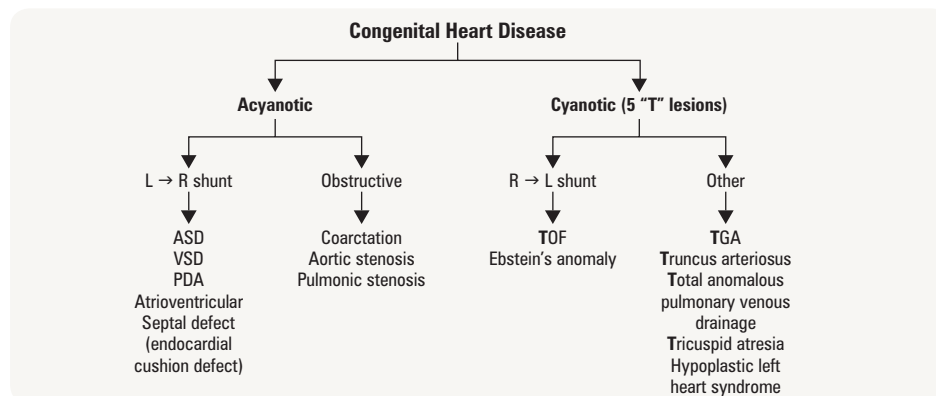


Figure 2. Common congenital heart diseases

## Acyanotic Congenital Heart Disease

### 1. LEFT TO RIGHT SHUNT LESIONS

- extra blood is displaced through a communication from the left to the right side of the heart → increased pulmonary blood flow → increased pulmonary pressures
- shunt volume is dependent upon three factors: (1) size of defect (2) pressure gradient between chambers or vessels (3) peripheral outflow resistance
- untreated shunts can result in pulmonary vascular disease, left ventricular dilatation and dysfunction, right ventricular hypertension and hypertrophy (RVH), and ultimately R to L shunts

#### Atrial Septal Defect (ASD)

- 3 types: *ostium primum* (common in Down syndrome), *ostium secundum* (most common type, 50-70%), *sinus venosus* (defect located at entry of superior vena cava into right atrium)
- epidemiology: 6-8% of congenital heart lesions
- natural history:
  - 80-100% spontaneous closure rate if ASD diameter <8 mm
  - if remains patent, congestive heart failure (CHF) and pulmonary hypertension can develop in adult life
- clinical presentation:
  - history: often asymptomatic in childhood
  - physical exam: grade 2-3/6 pulmonic outflow murmur, widely split and fixed S2
- investigations:
  - ECG: right axis deviation (RAD), mild RVH, right bundle branch block (RBBB)
  - CXR: increased pulmonary vasculature
- management: elective surgical or catheter closure between 2-5 yr of age

#### Ventricular Septal Defect (VSD)

- most common congenital heart defect (30-50%)
- small VSD (majority)
  - clinical presentation:
    - history: asymptomatic, normal growth, and development
    - physical exam: early systolic to holosystolic murmur, best heard at LLSB, thrill
  - investigations: ECG and CXR are normal
  - management: most close spontaneously

- moderate-to-large VSD
  - epidemiology: CHF by 2 mo; late secondary pulmonary hypertension if left untreated
  - clinical presentation
    - ♦ history: delayed growth, decreased exercise tolerance, recurrent URTIs or “asthma” episodes
    - ♦ physical exam: holosystolic murmur at LLSB, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur
  - investigations:
    - ♦ ECG: left ventricular hypertrophy (LVH), left atrial hypertrophy (LAH), RVH
    - ♦ CXR: increased pulmonary vasculature, cardiomegaly, CHF
  - management: treatment of CHF and surgical closure by 1 yr old



#### Moderate-to-large VSD

Size of VSD is inversely related to intensity of murmur.

### Patent Ductus Arteriosus (PDA)

- patent vessel between descending aorta and left pulmonary artery (normally, functional closure within first 15 h of life, anatomical closure within first days of life)
- epidemiology:
  - 5-10% of all congenital heart defects
  - delayed closure of ductus is common in premature infants (1/3 of infants <1750 g); this is different from PDA in term infants
- natural history: spontaneous closure common in premature infants, less common in term infants
- clinical presentation
  - history: asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use, CHF
  - physical exam:
    - ♦ tachycardia, bounding pulses, hyperactive precordium, wide pulse pressure, continuous “machinery” murmur best heard at left infraclavicular area
- investigations:
  - ECG: may show LAE, LVH, RVH
  - CXR: normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery
  - ECHO: diagnostic
- management
  - indomethacin (Indocin®): PGE2 antagonist (PGE2 maintains ductus arteriosus patency) is only effective in premature infants
  - catheter or surgical closure if PDA causes respiratory compromise, FTT, or persists beyond 3rd month of life



Figure 3. Patent ductus arteriosus (PDA)



#### Physical Exam for PDA (in term infant)

- Heavy “machinery” murmur
- High pulse rate
- Wide pulse pressure
- Hyperactive precordium
- Big bounding pulse

## 2. OBSTRUCTIVE LESIONS

- present with decreased urine output, pallor, cool extremities and poor pulses, shock or sudden collapse

### Coarctation of the Aorta

- definition: narrowing of aorta (almost always at the level of the ductus arteriosus)
- epidemiology: commonly associated with bicuspid aortic valve (50%); Turner syndrome (35%)
- clinical presentation
  - history: often asymptomatic
  - physical exam:
    - ♦ upper extremity systolic pressures of 140-145 mmHg
    - ♦ few have high BP in infancy (160-200 mmHg systolic), but this decreases as collaterals develop
    - ♦ decreased blood pressure and weak/absent pulses in lower extremities
    - ♦ radial-femoral delay
    - ♦ absent or systolic murmur with late peak at apex, left axilla, and left back
    - ♦ if severe, presents with shock in the neonatal period when the ductus closes
- investigations: ECG shows RVH early in infancy, LVH later in childhood
- prognosis: can be complicated by hypertension; if associated with other lesions (e.g. PDA, VSD) can lead to CHF
- management: give prostaglandins to keep ductus arteriosus patent for stabilization and perform surgical correction in neonates. For older infants and children balloon arterioplasty may be an alternative to surgical correction.

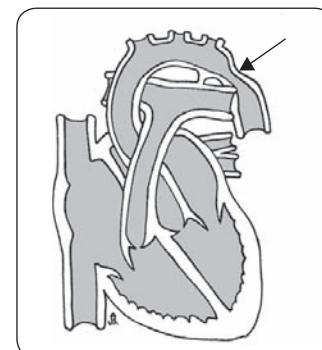


Figure 4. Coarctation of the aorta

### Aortic Stenosis

- 4 types: valvular (75%), subvalvular (20%), supravalvular and idiopathic hypertrophic subaortic stenosis (IHSS) (5%)
- clinical presentation
  - history: often asymptomatic, but may be associated with CHF, exertional chest pain, syncope or sudden death
  - physical exam: systolic ejection murmur (SEM) at RUSB with aortic ejection click at the apex (only for valvar stenosis)
- management: valvular stenosis is usually treated with balloon valvuloplasty, patients with subvalvular or supravalvular stenosis require surgical repair, exercise restriction required

## Pulmonary Stenosis

- 3 types: valvular (90%), subvalvular, or supra-valvular
- definition of critical pulmonic stenosis:
  - inadequate pulmonary blood flow, dependent on ductus for oxygenation, progressive hypoxia and cyanosis
- natural history: may be part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with syndromes (e.g. congenital rubella, Noonan syndrome)
- clinical presentation
  - history: spectrum from asymptomatic to CHF
  - physical exam: wide split S2 on expiration, SEM at LUSB, pulmonary ejection click (for valvular lesions)
- investigations:
  - ECG: RVH
  - CXR: post-stenotic dilation of the main pulmonary artery
- management: surgical repair if critically ill, or if symptomatic in older infants/children



### Causes of Cyanotic Heart Disease – Think 1,2,3,4,5

- ONE** big trunk (Truncus arteriosus)
- TWO** interchanged vessels (Transposition of the great vessels)
- THREE** leaflets (Tricuspid atresia)
- FOUR** anatomical abnormalities (Tetralogy of Fallot)
- FIVE** words (Total anomalous pulmonary venous return)

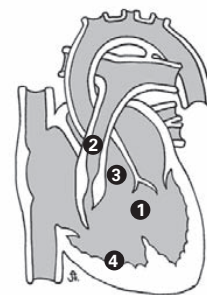


Figure 5. Tetralogy of Fallot (TOF)



### Tetralogy of Fallot

- Ventricular septal defect (VSD)
- Right ventricular outflow tract obstruction (RVOTO)
- Aortic root “overriding” VSD
- Right ventricular hypertrophy



### Ebstein's Anomaly

- Septal and posterior leaflets of tricuspid valve are malformed and displaced into the RV
- Potential for RV dysfunction, tricuspid stenosis, tricuspid regurgitation (TR) or functional pulmonary atresia if RV unable to open pulmonic valves
- Accessory conduction pathways (WPW) are often present

### Etiology

- Unknown, associated with maternal lithium and benzodiazepine use in 1st trimester

### Treatment

- Newborns: consider closure of tricuspid valve + aortopulmonary shunt, or transplantation
- Older children: tricuspid valve repair or valve replacement + ASD closure

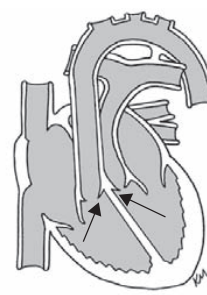


Figure 6. Transposition of the great arteries (TGA)

## Cyanotic Congenital Heart Disease

- systemic venous return re-enters systemic circulation directly
- most prominent feature is cyanosis ( $O_2$  sat <75%)
- hyperoxic test differentiates between cardiac and other causes of cyanosis
  - obtain preductal, right radial ABG in room air, then repeat after the child inspires 100%  $O_2$
  - if  $PaO_2$  improves to greater than 150 mmHg, cyanosis less likely cardiac in origin

### 1. RIGHT TO LEFT SHUNT LESIONS

#### Tetralogy of Fallot

- epidemiology: 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy with peak incidence at 2-4 mo of age
- pathophysiology:
  - embryological defect due to anterior and superior deviation of the outlet septum leading to: VSD, RVOTO (e.g. pulmonary stenosis), over-riding aorta and RVH
    - ♦ infants may initially have a L → R shunt (therefore no cyanosis); however, RVOTO is progressive, leading to increasing R → L shunting with hypoxemia and cyanosis
    - ♦ degree of RVOTO determines the direction and degree of shunt and, therefore, the extent of clinical cyanosis and degree of RVH
- clinical presentation
  - history: hypoxic “tet” spells
    - ♦ during exertional states (crying, exercise) the increasing pulmonary vascular resistance and decrease in systemic resistance causes an increase in right-to-left shunting
    - ♦ clinical features include paroxysm of rapid and deep breathing, irritability and crying, increasing cyanosis, decreased intensity of murmur (decreased flow across RVOTO)
    - ♦ if severe, can lead to decreased level of consciousness, seizures, death
  - physical exam
    - ♦ single loud S2 due to severe pulmonary stenosis (i.e. RVOTO), systolic ejection murmur (LSB)
- investigations:
  - ECG: RAD, RVH
  - CXR: boot shaped heart, decreased pulmonary vasculature, right aortic arch (in 20%)
- management of spells:  $O_2$ , knee-chest position, fluid bolus, morphine sulfate, propranolol
- treatment: surgical repair at 4-6 mo of age; earlier if marked cyanosis or “tet” spells

### 2. OTHER CYANOTIC CONGENITAL HEART DISEASES

#### Transposition of the Great Arteries (TGA)

- epidemiology: 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonate
- pathophysiology: parallel pulmonary and systemic circulations
  - systemic: body → RA → RV → aorta → body
  - pulmonary: lungs → LA → LV → pulmonary artery → lungs
  - survival is dependent on mixing through PDA and/or atrial or ventricular septal defects
- physical exam:
  - neonates: ductus arteriosus closure causes rapidly progressive severe hypoxemia unresponsive to oxygen therapy, acidosis, and death
  - VSD present: cyanosis is not prominent; CHF within first weeks of life
  - VSD absent: no murmur
- investigations:
  - ECG: RAD, RVH, or may be normal
  - CXR: egg-shaped heart with narrow mediastinum (“egg on a string”)

- **management:**
  - symptomatic neonates: prostaglandin E1 infusion to keep ductus open until balloon atrial septostomy
  - surgical repair: arterial switch performed in the first two weeks in those without a VSD while LV muscle is still strong

### Total Anomalous Pulmonary Venous Connection

- epidemiology: 1-2% of CHD
- pathophysiology:
  - all pulmonary veins drain into right-sided circulation (systemic veins, RA)
  - no direct oxygenated pulmonary venous return to left atrium
  - often associated with obstruction at connection sites
  - ASD must be present for oxygenated blood to shunt into the LA and systemic circulation
- **management:** surgical repair in all cases and required urgently for severe cyanosis

### Truncus Arteriosus

- pathophysiology:
  - single great vessel gives rise to the aorta, pulmonary and coronary arteries
  - truncal valve overlies a large VSD
  - potential for coronary ischemia with fall in pulmonary vascular resistance
- management: surgical repair within first 6 wk of life

### Hypoplastic Left Heart Syndrome (HLHS)

- epidemiology: 1-3% of CHD; commonest cause of death from CHD in first month of life
- pathophysiology: LV hypoplasia may include atretic or stenotic mitral and/or aortic valve, small ascending aorta, and coarctation of the aorta with resultant systemic hypoperfusion
- systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
- management:
  - intubate and correct metabolic acidosis
  - IV infusion of PGE1 to keep ductus open
  - surgical palliation (overall survival 50% to late childhood) or heart transplant



#### 4 Features of Hypoplastic LHS

- Hypoplastic LV
- Narrow mitral/aortic valves
- Small Ascending Aorta
- Contracted Aorta

## Congestive Heart Failure (CHF)

- see [Cardiology](#), C30

### Etiology

- CHD
- arteriovenous malformations (AVMs)
- cardiomyopathy
- arrhythmias
- acute hypertension
- anemia
- cor pulmonale
- myocarditis

### History

- infant: feeding difficulties, early fatigability, diaphoresis while sleeping or eating, respiratory distress, lethargy, FTT
- child: decreased exercise tolerance, fatigue, decreased appetite, failure to thrive, respiratory distress, frequent URTIs or "asthma" episodes
- orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all uncommon in children

### Physical Findings

- 4 key features: tachycardia, tachypnea, cardiomegaly, hepatomegaly
- FTT
- alterations in peripheral pulses, four limb blood pressures (in some CHDs)
- dysmorphic features associated with congenital syndromes

### Investigations

- CXR: cardiomegaly, pulmonary venous congestion

### Management

- general: sitting up, O<sub>2</sub>, sodium and water restriction, increased caloric intake
- pharmacologic: diuretics, afterload reduction (i.e. ACE inhibitor), digoxin rarely used
- curative: correction of underlying cause



#### 4 Key Features of CHF

##### 2 Tachy's and 2 Megaly's

- Tachycardia
- Tachypnea
- Cardiomegaly
- Hepatomegaly

## Dysrhythmias

- see [Cardiology](#), C12
- can be transient or permanent, congenital (structurally normal or abnormal) or acquired (toxin, infection, infarction)

### Sinus Arrhythmia

- phasic variations with respiration (present in almost all normal children)

### Sinus Tachycardia

- rate of impulses arising from sinus node is elevated (>150 bpm in infants, >100 bpm in older children)
- etiology: hypertension, fever, anxiety, sepsis, anemia/hypoxia, PE, drugs, etc.
- differentiate from SVT (see below) by slowing the sinus rate (vagal massage,  $\beta$ -blockers) to identify sinus P waves

### Premature Atrial Contractions (PACs)

- may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitalis toxicity

### Premature Ventricular Contractions (PVCs)

- common in adolescents
- benign if single, uniform, disappear with exercise, and no associated structural lesions
- if not benign, may degenerate into more severe dysrhythmias

### Supraventricular Tachycardia (SVT)

- abnormally rapid heart rhythm originating above the ventricles – most frequent sustained dysrhythmia in children
- not life-threatening, but can lead to symptoms

### Complete Heart Block

- congenital heart block can be caused by maternal anti-Ro or anti-La (e.g. mother with SLE)
- often diagnosed in utero (may lead to development of fetal hydrops)
- clinical symptoms related to level of block (the lower the block, the slower the heart rate and greater the symptoms of inadequate cardiac output)
- symptomatic patients need a pacemaker



#### Pediatric vs. Adult ECG

Pediatric ECG findings that may be normal:

- HR >100 bpm
- Shorter PR, QT intervals and QRS duration
- Inferior and lateral small Q waves
- RV larger than LV in neonates, so normal to have:
  - Right axis deviation
  - Large precordial R waves
  - Upright T waves
  - Inverted T waves in the anterior precordial leads from early infancy to teen years

## Heart Murmurs

- 50-80% of children have audible heart murmurs at some point in their childhood
- most childhood murmurs are functional (e.g. “innocent”) without associated structural abnormalities and have normal ECG and radiologic findings
- in general, murmurs can become audible or accentuated in high output states, e.g. fever, anemia



**Table 11. Differentiating Heart Murmurs**

	Innocent	Pathological
<b>History and Physical</b>	Asymptomatic	Symptoms and signs of cardiac disease (FIT, exercise intolerance)
<b>Timing</b>	SEM	All diastolic, pansystolic, or continuous (except venous hum)
<b>Grade</b>	<3/6	≥3/6 (palpable thrill)
<b>Splitting</b>	Physiologic S2	May have fixed split or single S2
<b>Extra sounds/Clicks</b>	None	May be present
<b>Change of Position</b>	Murmur varies	Unchanged

**Table 12. Five Innocent Heart Murmurs**

Type	Description	Age	Differential Diagnosis
<b>Peripheral Pulmonic Stenosis</b>	Neonates, low-pitched, radiates to axilla and back	Neonates, usually disappears by 3-6 mo	Patent Ductus Arteriosus Pulmonary stenosis
<b>Still's Murmur</b>	Vibratory, LLSB or apex, SEM	3-6 yr	Subaortic stenosis Small ventricular septal defect
<b>Venous Hum</b>	Infraclavicular hum, continuous, R>L	3-6 yr	Patent Ductus Arteriosus
<b>Pulmonary Ejection</b>	Soft, blowing, LUSB, SEM	8-14 yr	Atrial septal defect Pulmonary stenosis
<b>Supraclavicular Arterial Bruit</b>	Low intensity, above clavicles	Any age	Aortic stenosis Bicuspid aortic valve

## Infective Endocarditis

- see [Infectious Diseases](#), ID17



## Development



### Approach to Global Developmental Delay

- also known as Early Developmental Impairment (EDI)

#### Definition

- performance significantly below average in two or more areas of development (i.e. gross motor, fine motor, language, cognitive, social, adaptive)
- when persistent, these become developmental disabilities which are lifelong impairments

#### Epidemiology

- 5-10% of children have neurodevelopmental delay
- careful evaluation can reveal a cause in 50-70% of cases

#### Etiology

- CNS abnormalities (meningitis/encephalitis, brain malformation, trauma, etc.)
- sensory deficits (hearing, vision)
- environmental (psychosocial neglect, lead exposure, antenatal drug or alcohol exposure, etc.)
- genetic/chromosomal disorders (Down syndrome, Fragile X, etc.)
- metabolic disorders (inborn errors of metabolism, hypothyroidism, etc.)
- obstetrical (prematurity, hypoxic ischemic encephalopathy, TORCH infections, etc.)

#### Clinical Presentation

- history
  - intrauterine exposures, perinatal events
  - detailed developmental milestones: rate of acquisition, regression of skills
  - associated problems: feeding, seizures, behaviour, sleep
  - family history, consanguinity
  - social history
- physical
  - dysmorphic features, hepatosplenomegaly, neurocutaneous markers, growth parameters, detailed neurological examination
- investigations
  - neurodevelopmental assessment, vision and hearing test, psychosocial evaluation, OT, PT and/or SLP assessments, genetics consultation
  - laboratory testing and imaging (guided by history and physical exam)
    - ♦ microarray, chromosomes, FISH, Fragile X testing, neuroimaging, metabolic workup, neuroelectrophysiologic testing

#### Management

- dependent on specific area of delay
- therapy services (e.g. speech and language therapy for language delay, OT and/or PT for motor delay), early intervention services (e.g. infant development services, Ontario Early Years Centres)



## Intellectual Disability

### Definition

- state of functioning that begins in childhood and is characterized by limitations in both intelligence and adaptive skills
- referred to as mental retardation in DSM-IV, not a term used in clinical settings
- historically defined as an IQ <70

### Epidemiology

- 1% of general population; M:F = 1.5:1

### Etiology

- any disorder that interferes with brain development and functioning
- prenatal (majority): TORCH infections, fetal alcohol syndrome
- genetic/metabolic: DS, Fragile X, PKU, untreated or delayed diagnosis of congenital hypothyroidism, CNS abnormalities, other chromosomal/metabolic disorders

### Risk Factors

- male, consanguineous parents, family history, older maternal age, decreasing maternal education, certain ethnicities
- prenatal: pre-eclampsia, maternal malnutrition or DM
- perinatal: prematurity, low birth weight, birth trauma/hypoxia
- postnatal: intracranial hemorrhage, CNS or other serious infection, hypoxia, environmental toxins, psychosocial deprivation, malnutrition

### Clinical Presentation

- history
  - well below average general intellectual functioning
  - significant deficits in adaptive functioning in at least two of: communication, self-care, home-living, social skills, self-direction, academic skills, work, leisure, health, safety
- physical
  - check growth, dysmorphic features, complete physical exam
- investigations
  - standardized psychology assessment (includes IQ test and measure of adaptive functioning)
  - vision, hearing, and neurologic assessment
  - genetic and metabolic testing as indicated

### Management

- main objective: enhance adaptive functioning level
- requires an interprofessional team with strong case co-ordination
- emphasize community-based treatment and early intervention
- individual/family therapy, behaviour management services, therapy services (e.g. OT, SLP), medications for associated conditions
- education: life skills, vocational training, communication skills, family education
- psychosocial support for individual and family; respite care

### Prognosis

- higher rates of sensory deficits, motor impairment, behavioural/emotional disorders, seizures, psychiatric illness



#### DSM-IV Criteria for Intellectual Disability

- Significant sub-average intellectual function
- Significant limitations in adaptive function
- Onset before 18 yr old



#### Classification of Intellectual Disability

Severity	% Cases	IQ
Mild	85	50-70
Moderate	10	35-49
Severe	3-4	20-34
Profound	1-2	<20

## Language Delay

### Definition

- no universally accepted definition, but often identified around 18 mo of age with enhanced well baby visit
- if formally tested, performance on a standardized assessment of language is at least one standard deviation below mean of age
- can be expressive, receptive, or both
- expressive language: ability to produce or use language
- receptive language: ability to understand language

### Epidemiology

- ~10-15% of 2 yr old children have a language delay, but only 4-5% remain delayed after 3 yr of age
- ~6-8% of school-aged children have specific language impairment (many of whom were not identified before school entry)

## Etiology

- cognitive disability
- constitutional language delay
- genetic/metabolic: DS, Fragile X syndrome, Williams syndrome, hypothyroidism, PKU, etc.
- hearing impairment
- mechanical problems: cleft palate, cranial nerve palsy
- medical condition: seizure disorder (includes acquired epileptic aphasia), CP, TORCH infection, iron deficiency, lead poisoning, etc.
- autism spectrum disorder (ASD)
- psychosocial: neglect or abuse
- selective mutism

## Risk Factors

- male, positive family history, prematurity, psychosocial (poverty, low parental education, maternal depression)

## Clinical Presentation

- history
  - concerns about hearing, delay in language development or regression in previously normal language development
  - delayed language milestones on well-child check up; presence of red flags
  - must determine if language delay is expressive, receptive or mixed
  - children with expressive language delays may have concurrent behaviour problems or drooling (because of abnormal oral musculature)
  - risk factors for hearing loss (hereditary, recurrent AOM) and language delay
- physical
  - guided by history: look for abnormal growth, dysmorphisms, unusual social interactions (lack of eye contact, not pointing)
  - include full exam of the external/internal ear (e.g. TM scarring), oral pharynx (e.g. cleft palate) and neurologic system (including tone)
- investigations
  - use of language specific screens in primary care setting: The Early Language Milestone, CAT/CLAMS, MCHAT, etc.
  - all children with suspected language delay MUST be referred to an audiologist for a hearing assessment
  - CBC (to rule out anemia), venous blood lead levels, genetic/metabolic workup as indicated

## Management

- specific to etiology
- often multidisciplinary and requires appropriate referrals: early intervention services, special education services, SLP, ENT and dental professionals, general support services
- primary care provider can help reinforce family's understanding of delay and provide follow-up and care coordination
- prevention: parents can read aloud to their child, engage in dialogic reading, avoid baby talk, narrate daily activities, etc.

## Prognosis

- depends on etiology
- if language delay persists beyond 5 yr old then more likely to have difficulties in adulthood
- persistent language delay is associated with poor academic performance, behavioural problems, social isolation



### Risk Factors for Sensorineural Hearing Loss

- Genetic syndromes/family history
- Congenital (TORCH) infections
- Craniofacial abnormalities
- <1,500 g birthweight
- Hyperbilirubinemia/kernicterus
- Asphyxia/low APGAR scores
- Bacterial meningitis, viral encephalitis



Bilingual exposure generally does NOT explain a frank delay in language development.



Primary care physicians should suspect a receptive language delay in any young child with an expressive language delay.

## Fetal Alcohol Spectrum Disorder (FASD)



### Definition

- term describing the range of effects of prenatal exposure to alcohol, including physical, mental, behavioural and learning disabilities
- no "safe" level of alcohol consumption during pregnancy has been established
- spectrum includes: Fetal Alcohol Syndrome (FAS), partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Birth Defects (ARBD), and Alcohol-Related Neurodevelopmental Disorder (ARND)

### Epidemiology

- prevalence of FAS and FASD is 0.1% and 1.0%, respectively
- most common preventable cause of intellectual disability

### Pathogenesis

- specific mechanism of FASD is unknown, but hypothesis include nutritional deficits, toxic effects of acetaldehyde, alteration of placental transport, abnormal protein synthesis, and altered cerebral neurotransmitter

**Diagnosis**

- often misdiagnosed or missed entirely
- diagnosis of FAS, ARBD and ARND all require evidence of maternal drinking during pregnancy
- criteria for diagnosis of FAS
  - a) growth deficiency: low birth weight and/or decelerating weight over time not due to nutrition
  - b) characteristic pattern of facial anomalies: short palpebral fissures, flattened philtrum, thin upper lip, flat midface
  - c) central nervous system dysfunction: microcephaly and/or neurobehavioural dysfunction (hyperactivity, fine motor problems, attention deficits, learning disabilities, cognitive disabilities, difficulties in adaptive functioning, etc.)
- criteria for diagnosis of ARBD
  - a) congenital anomalies, including malformations and dysplasias of the cardiac, skeletal, renal, ocular, and auditory systems
- criteria for diagnosis of ARND
  - a) central nervous system dysfunction (similar to FAS)
  - b) complex pattern of behavioural or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone

**Management**

- early diagnosis is essential to prevent secondary disabilities
- no cure, but individuals with FASD and their families should be linked to community resources and services to improve outcome

**Prognosis**

- secondary disabilities include unemployment, mental health problems, difficulties with the law, inappropriate sexual behaviour, disrupted school experience, peer problems

## Learning Disabilities

**Definition**

- specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
- a significant discrepancy between a child's intellectual ability and their academic performance
- several types or ADLs: learning disabilities in reading, writing, mathematics

**Epidemiology**

- prevalence: 2-10%
- high incidence of psychiatric comorbidity: anxiety, dysthymia, conduct disorder (CD), major depressive disorder (MDD), oppositional defiant disorder (ODD), attention deficit hyperactivity disorder (ADHD)

**Etiology**

- pathogenesis is unknown, likely genetic factors involved
- learning disabilities may be associated with a number of conditions:
  - genetic/metabolic: Turner syndrome, Klinefelter syndrome
  - perinatal: prematurity, low birth weight, birth trauma/hypoxia
  - postnatal: CNS damage, hypoxia, environmental toxins, FAS, psychosocial deprivation (understimulation), malnutrition
- poor visual acuity is NOT a cause

**Risk Factors**

- positive family history, prematurity, other developmental and mental health conditions, neurologic disorders (e.g. seizure disorders, neurofibromatosis), history of CNS infection/irradiation/traumatic injury

**Clinical Presentation**

- history and physical
  - school difficulties (academic achievement, behaviour, attention, social interaction)
  - development of negative self-concept → reluctance to participate even in areas of strength
  - social issues: overt hostility towards parents/teachers; difficulties making friends for several reasons (problems remembering names, difficulties with language to engage in conversations, inability to understand games and complex rules, etc.), bullying and anxiety
  - look for dysmorphisms, complete physical exam
- investigations
  - standardized tests for IQ
  - individual scores on achievement tests in reading, mathematics or written expression (WISC III, WRAT) >2 SD below that expected for age, education, and IQ

## Management

- provide quality instruction for specific learning disability
- support student by modifying the curriculum and/or providing accommodations (e.g. scribe for writing, extra time for tests, photocopied notes, etc.)
- consider grade retention in certain students (no guidelines exist, very rare in Ontario)
- specialized education placements that can provide educational remediation

## Prognosis

- limited information available about persistence of learning disabilities over time
- low self-esteem, poor social skills, 40% school drop-out rate

## Motor Delay

- see *Cerebral Palsy*, P90 and *Muscular Dystrophy*, P44

## Endocrinology



## Anti-Diuretic Hormone

### Diabetes Insipidus (DI)

- see [Endocrinology](#), E19 and [Nephrology](#), NP11



### Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

- see [Endocrinology](#), E19 and [Nephrology](#), NP9



## Diabetes Mellitus (DM)

### DM Type 1

- insulin deficiency following destruction of the pancreatic  $\beta$  cells



### Epidemiology

- most common form of diabetes mellitus in children, M=F
- variable prevalence internationally, affects ~1:4000 children in Canada
- can present at any age, but bimodal peaks at 5-7 yr old and at puberty

### Etiology

- type 1A: cell-mediated autoimmune destruction of  $\beta$ -cells of the pancreas
- type 1B: rare, non-immune variation; unknown cause
- disease results from some level of genetic predisposition and an environmental trigger
  - HLA locus confers ~50% of genetic susceptibility
  - trigger likely infectious and/or hormonal (as suggested by bimodal peaks in age of onset)

### Risk Factors

- positive family history of DM1, personal or family history of other autoimmune diseases

### Clinical Presentation

- history
  - initially presents as polyuria, often manifested as nocturia or secondary enuresis
  - polydipsia, weight loss (lack of insulin leading to a catabolic state) and polyphagia
  - diabetic ketoacidosis on initial presentation (~20%): vomiting, abdominal pain, confusion/lethargy
- physical
  - tachypnea, signs of dehydration,  $\downarrow$  LOC, Kussmaul's respiration, ketone breath
- investigations
  - initial tests: urine dipstick (glucose, ketones), random blood glucose ( $>11.1$ )
  - DKA bloodwork: venous/arterial blood gas, osmolarity, plasma glucose, bicarbonate, HbA1C, serum ketones, BUN, Cr, electrolytes, CBC
  - if etiology is unclear, consider ordering autoimmune antibodies (anti-Gad, anti-islet)

### Management

- disclose diagnosis and prompt patient education around survival skills, meal plans and insulin injections
- refer patient to facility capable of managing DM1
- management is multi-disciplinary and family-centered
- initial insulin dosing
  - 2/3 of total daily insulin dose in AM (1/3 rapid acting + 2/3 intermediate-acting)
  - 1/3 of total daily insulin dose in PM (1/3 rapid acting + 2/3 intermediate-acting)

### Diagnostic Criteria for Diabetes Mellitus (Types 1 and 2)

One of:

- HbA1C  $\geq 6.5\%$  (not validated in children)
- Fasting glucose  $\geq 7.0$  mmol/L
- 2 h plasma glucose during OGTT  $\geq 11.1$  mmol/L
- Random glucose  $\geq 11.1$  mmol/L with classic symptoms of hyperglycemia (polyuria, polydipsia, weight loss)



### Blood Glucose Targets by Age

Age range	Pre-meal blood glucose target	HbA1c target
<6	6-12	<8.5%
6-12	6-10	<8%
>12	4-7	<7%

- blood glucose monitoring
  - tight glycemic control decreases rate of long term complications
  - target glucose range: in infants/toddlers from 6-10 mmol/L, in children 4-10 mmol/L, in adolescents 4-7 mmol/L
  - for tighter control, may consider continuous subcutaneous insulin infusion (CSII) pump or MDI (multiple daily injections regimen: basal insulin plus analog for meals)
  - young children are more susceptible to hypoglycemia
- if DKA present: ABCs, admit, correct dehydration, correct acidosis (start insulin infusion), restore normal blood glucose, identify/treat precipitating event
  - low threshold to investigate (CT/MRI) and treat DKA, as cerebral edema is a major concern
  - see [Endocrinology](#), E11
- screen for micro- and macrovascular complications (regular ophthalmology assessments, blood pressure, urine microalbuminemia), concurrent autoimmune diseases (thyroiditis, celiac disease, etc.) and mental health issues (depression, eating disorders)



### Prognosis

- no cure currently
- short-term complications
  - hypoglycemia: due to missed/delayed meals, excess insulin or exercise, illness; can lead to seizures and/or coma; reversed with PO/IV glucose or IM glucagon
  - hyperglycemia: due to intercurrent illness, diet-to-insulin mismatch, ↑ risk of end-organ damage
  - DKA: due to missed insulin doses, infection; most common cause of death
- long-term complications
  - microvascular: retinopathy, nephropathy, neuropathy
  - macrovascular: metabolic syndrome
  - increased risk of other autoimmune diseases

### DM Type 2

- see [Family Medicine](#), FM22, [Endocrinology](#), E6
- impaired glucose metabolism due to increased peripheral insulin resistance
- rare before 10 yr of age, but more common in older children/adolescents
- prevalence is rising mainly due to the increased incidence of childhood obesity
- risk factors: obesity, positive family history, female gender, certain ethnic groups
- clinical presentation may be similar to that of DM1, though most children are asymptomatic
- may present in DKA or hyperglycemic hyperosmotic nonketotic (HONK) state
- management: diet, physical activity (60 min of moderate to intense exercise per day, limit non-academic screen time to 2 h/d), weight loss, oral hypoglycemics (metformin used in children because it does not cause hypoglycemia), insulin
- prognosis: includes microvascular and macrovascular complications similar to DM1



## Growth

### APPROACH TO SHORT STATURE

#### Definition

- short stature – height <3rd percentile
- poor growth evidenced by growth deceleration (height crosses major percentile lines, growth velocity <25th percentile)

#### Epidemiology

- ~2.5% of the population by definition

#### Etiology

- see sidebar

#### Clinical Presentation

- history and physical
  - plot on growth curve (special growth charts available for Turner syndrome, achondroplasia, DS)
  - decreased growth velocity may be more worrisome than actual height
  - see Figure 7 for the approach to short stature
- investigations
  - calculate mid-parental height: children are usually in a percentile between their parents' height (see *Mid-Parental Height* sidebar, P10)
  - AP x-ray of left hand and wrist for bone age
  - remaining investigations guided by history and physical (e.g. TSH, sweat chloride, etc.)



#### Short Stature DDx

##### ABCDEFG

**A**lone (neglected infant)  
**B**one dysplasias (rickets, scoliosis, mucopolysaccharidoses)  
**C**hromosomal (Turner, Down)  
**D**elayed growth (constitutional)  
**E**ndocrine (low growth hormone, Cushing, hypothyroid)  
**F**amilial  
**G**I malabsorption (celiac, Crohn's)



#### 4 Questions to Ask when Evaluating Short Stature

- Was there IUGR?
- Is the growth proportionate?
- Is the growth velocity normal?
- Is bone age delayed?

## Management

- depends on severity of problem as perceived by parents/child
- no treatment for non-pathological short stature, except for idiopathic short stature
- GH therapy if requirements met (see *Growth Hormone Deficiency*, below)
- other conditions that are treated: Turner, Prader-Willi, chronic renal failure
- support and management of resultant self-image issues, social anxiety, etc.



To check for proportionality, measure upper to lower segment ratio (U/L) using the pubic symphysis as your landmark. Normals are 1.7 for newborn, 1.4 for young child, 0.9 for adult male, 1.0 for adult female.

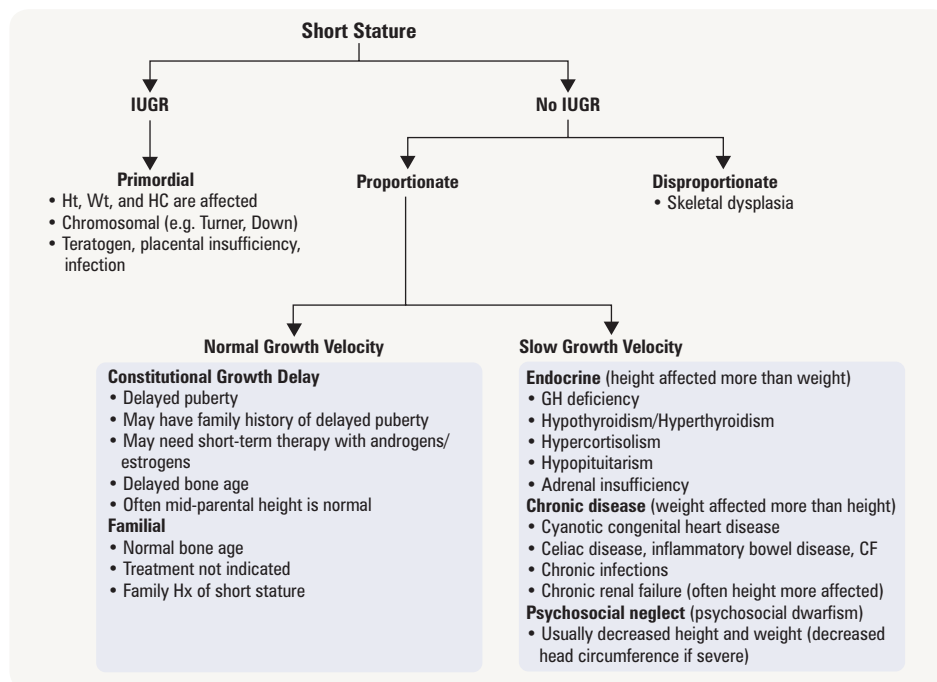


Figure 7. Approach to the child with short stature

## GROWTH HORMONE (GH) DEFICIENCY

- a rare but treatable cause of short stature in children

### Epidemiology

- 1/10,000-1/4,000 children

### Etiology

- GH important for chondrocyte proliferation and IGF-1 release → IGF-1 acts at long bones, liver
- congenital GH deficiency: idiopathic, embryologic CNS malformation (associated with midline facial anomalies, neurologic defects, micropenis in males, hypoglycemia), perinatal asphyxia, rare mutations
- acquired GH deficiency: tumours (e.g. craniopharyngioma), trauma, cranial infection, irradiation, post-surgical

### Risk Factors

- previous head trauma, history of intracranial bleed or infection, head surgery or irradiation, positive family history, breech delivery

### Clinical Presentation

- history and physical
  - congenital: growth may be normal in first 6 mo (insulin main growth factor), growth deceleration after; look for micropenis
  - acquired: severe growth failure, ↑ weight/height ratio (short and chubby), infantile fat distribution, immature face with underdeveloped nasal bridge and frontal bossing, high-pitched voice, sparse and thin hair growth, delayed puberty
  - hypothalamic: pituitary dysfunction (micropenis, cryptorchidism, optic nerve hypoplasia, etc.)
- investigations
  - blood glucose (hypoglycemia), AP x-ray of left hand and wrist for bone age (delayed), IGF-1
  - testing for GH deficiency (stimulation testing), only performed when
    - ♦ height <3rd percentile
    - ♦ decreased growth velocity
    - ♦ midline craniofacial anomalies
    - ♦ episodes of hypoglycemia
    - ♦ delayed bone age, puberty



- physiologic increase in GH with arginine, clonidine, insulin, dopamine, or propranolol
- positive test if failure to raise GH  $>5.7$  ng/mL post-stimulation

**Management**

- GH therapy indicated if
  - GH shown to be deficient by 2 different stimulation tests
  - growth velocity  $<3$ rd percentile or height  $<<3$ rd percentile
  - bone age x-rays show unfused epiphyses/delayed bone age
  - Turner syndrome, Noonan syndrome, Prader-Willi syndrome, chronic renal failure, idiopathic short stature
- support and management of resultant self-image issues, social anxiety, etc.

**Prognosis**

- if administered at an early age, GH therapy can help patients achieve adult height
- children treated with recombinant GH are at a slightly increased risk of developing pseudotumor cerebri, slipped capital femoral epiphysis and worsening scoliosis
- rare side effects: pancreatitis, transient gynecomastia, increase of growth/pigmentation of nevi

**TALL STATURE**

- height greater than two SD above the mean for a given age, sex and race

**Etiology**

- constitutional/familial
- endocrine: Beckwith-Wiedemann syndrome, hyperthyroidism, hypophyseal gigantism, precocious puberty
- genetic: homocystinuria, Klinefelter syndrome, Marfan syndrome, Sotos syndrome

## Hypercalcemia/Hypocalcemia/Rickets

- see [Endocrinology](#), E39, E40, E45



## Hyperthyroidism and Hypothyroidism

- may be congenital or acquired (for acquired causes, see [Endocrinology](#), E22 and 27)

**CONGENITAL HYPERTHYROIDISM**

- also known as neonatal Graves' disease

**Epidemiology**

- $\sim 1:25,000$  neonates, M=F

**Etiology**

- results from transplacental passage of maternal thyroid stimulating antibodies from mother with a history of Graves' disease

**Clinical Presentation**

- history and physical
  - clinical manifestations may be masked if mother on antithyroid treatment
  - may present with tachycardia with congestive heart failure, heart murmur, goiter, craniosynostosis, irritability, poor feeding, FTT
- investigations
  - serum levels of TSH and free T4 in all infants with suspected congenital hypothyroidism or infants born to mothers with Graves' disease

**Management**

- methimazole until antibodies cleared
- symptomatic treatment as needed (e.g.  $\beta$ -blockers to control tachycardia)

**Prognosis**

- if prompt and adequate treatment given, most neonates improve rapidly
- antibodies usually spontaneous cleared by 2-3 mo of life
- fetal or neonatal hyperthyroidism may have adverse effects on CNS development, leading to developmental and behaviour problems

## CONGENITAL HYPOTHYROIDISM

### Epidemiology

- incidence: 1:4000-1:2000 newborns births; F:M=2:1
- one of the most common preventable causes of intellectual disability

### Etiology

- may be classified as permanent primary, central and transient hypothyroidism
- ~85% of primary cases are sporadic (mostly thyroid dysgenesis), remaining 15% hereditary (mostly inborn errors of thyroid synthesis)
- causes of transient hypothyroidism: maternal antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications

### Clinical Presentation

- history and physical
  - usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  - may have: prolonged jaundice, constipation, sluggish, hoarse cry, lethargy, poor feeding, macroglossia, coarse facial features, large fontanelles, umbilical hernia
- investigations
  - diagnosis through newborn screening of TSH or free T4; abnormal results should be confirmed with serum levels from venipuncture

### Management

- thyroxine replacement

### Prognosis

- excellent outcome if treatment started within 1-2 mo of birth
- if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or disability (mild to profound)

## Sexual Development

### AMBIGUOUS GENITALIA

#### Definition

- newborn or child whose gender is difficult to assign based on the appearance of genitalia
- subtype of disorders of sex differentiation (DSD): a condition in which development of chromosomal, gonadal or anatomic sex is atypical
- subtypes: 46,XX DSD, 46,XY DSD, ovotesticular DSD (true hermaphrodite)

#### Epidemiology

- incidence of genital abnormalities at birth is as high as 1:300
- prevalence of complex anomalies with true sexual ambiguity much lower at ~1:5000

#### Etiology

- 46,XY DSD
  - inborn error of testosterone biosynthesis or Leydig cell hypoplasia
  - 5- $\alpha$ -reductase deficiency, androgen receptor deficiency or insensitivity
  - luteinizing hormone (LH)/hCG unresponsiveness
- 46,XX DSD
  - virilizing congenital adrenal hyperplasia (CAH) (most common)
  - maternal source: virilizing ovarian or adrenal tumours, untreated maternal CAH, placental aromatase deficiency
- ovotesticular DSD
  - both ovarian follicles and seminiferous tubules in the same patient with a 46,XX karyotype
  - mixed gonadal dysgenesis

#### Risk Factors

- parental consanguinity, positive family history of ambiguous genitalia, early childhood illness/death or primary amenorrhea, maternal medications during pregnancy (androgens, progesterones, danazol, phenytoin, aminoglutethimide, endocrine disruptors)

#### Clinical Presentation

- history
  - thorough obstetrical history, including prenatal screens and maternal medications
  - family history: autosomal recessive pattern may suggest CAH, X-linked recessive pattern may suggest androgen insensitivity syndrome

- physical
  - male pseudohermaphrodite (XY): small phallus, hypospadias, undescended testicles
  - female pseudohermaphrodite (XX): clitoral hypertrophy, labioscrotal fusion
  - look for concurrent midline defects, dysmorphic features and congenital abnormalities
- investigations
  - karyotype and genetic work-up as indicated
  - blood work: electrolytes and renin (evidence of salt-wasting in CAH); 17-OH-progesterone, androgens, FSH and LH
  - imaging: abdominal U/S to look for uterus, testicles, ovaries

### Management

- depends on underlying etiology
- avoid announcement of probable sex or use of personal pronouns until all tests are complete
- continuous psychosocial support for parents and child during development
- elective surgical reconstruction of genitalia is sometimes possible

## CONGENITAL ADRENAL HYPERPLASIA (CAH)

### Definition

- autosomal recessive disorder characterized by the partial or total defect of various synthetic enzymes of the adrenal cortex required for cortisol and aldosterone production

### Epidemiology

- occurs in ~1:15,000 live births
- most common cause of ambiguous genitalia

### Etiology

- for biosynthetic pathways of adrenal cortex, see [Endocrinology](#), E29
- 21-hydroxylase deficiency (21-OH) responsible for ~95% of CAH cases
- results in ↓ cortisol and aldosterone production with shunting toward ↑↑ androgens
- cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
- rarer causes include deficiencies in 11-OH, cholesterol desmolase, 17-OH and 3-HSD



### Clinical Presentation

- depends on which enzyme in cortisol synthesis pathway is defective
- presentation of 21-OH deficiency can be divided into:
  - classic deficiency with salt wasting: inadequate aldosterone resulting in FTT, hyperkalemia, hyponatremia, hypoglycemia, acidosis
  - classic deficiency without salt wasting: simple virilizing type
  - non-classic: signs/symptoms of androgen excess (amenorrhea, precocious puberty, etc.)
- 21-OH deficiency screening is part of many newborn screening programs across North America
- high serum levels of 17-OH progesterone in random blood sample diagnostic for 21-OH deficiency

### Management

- correct any abnormalities in fluids, electrolytes or serum glucose
- provide glucocorticoids/mineralcorticoids as necessary, extra glucocorticoids in times of stress
- psychosocial support

### Prognosis

- complications if untreated include virilization, acne, salt wasting, hypotension

## NORMAL PUBERTAL DEVELOPMENT

### Physiology

- puberty occurs with the maturation of the hypothalamic–pituitary–gonadal (HPG) axis
- ↑ pulsatile release of GnRH → ↑ release of LH and FSH → maturation of gonads, release of sex steroids → secondary sexual characteristics
- adrenal production of androgens also required

### Females

- onset: age 8-13 yr old (may start as early as 7 yr in girls of African descent)
- usual sequence (Figure 8)
  1. thelarche: breast budding
  2. pubarche: axillary hair, body odour, mild acne
  3. growth spurt
  4. menarche: mean age 12.5 yr; indicates that growth spurt is almost complete; menses may be irregular in duration and length of cycle
- early puberty is common and often constitutional, late puberty is rare (rule out organic causes)

## Males

- onset: age 9-14 yr old
- usual sequence
  1. testicular enlargement
  2. penile enlargement
  3. pubarche: axillary and facial hair, body odour, mild acne
  4. growth spurt: occurs later in boys
- early puberty is uncommon (rule out organic causes), late puberty is common and often constitutional
- gynecomastia (transient development of breast tissue) is a common self-limited condition seen in 50% of male during puberty (but any discharge from nipple or fixed mass should be investigated)

## Tanner Staging

- scale used in paediatrics that defines physical measurements of development based on external primary and secondary sex characteristics

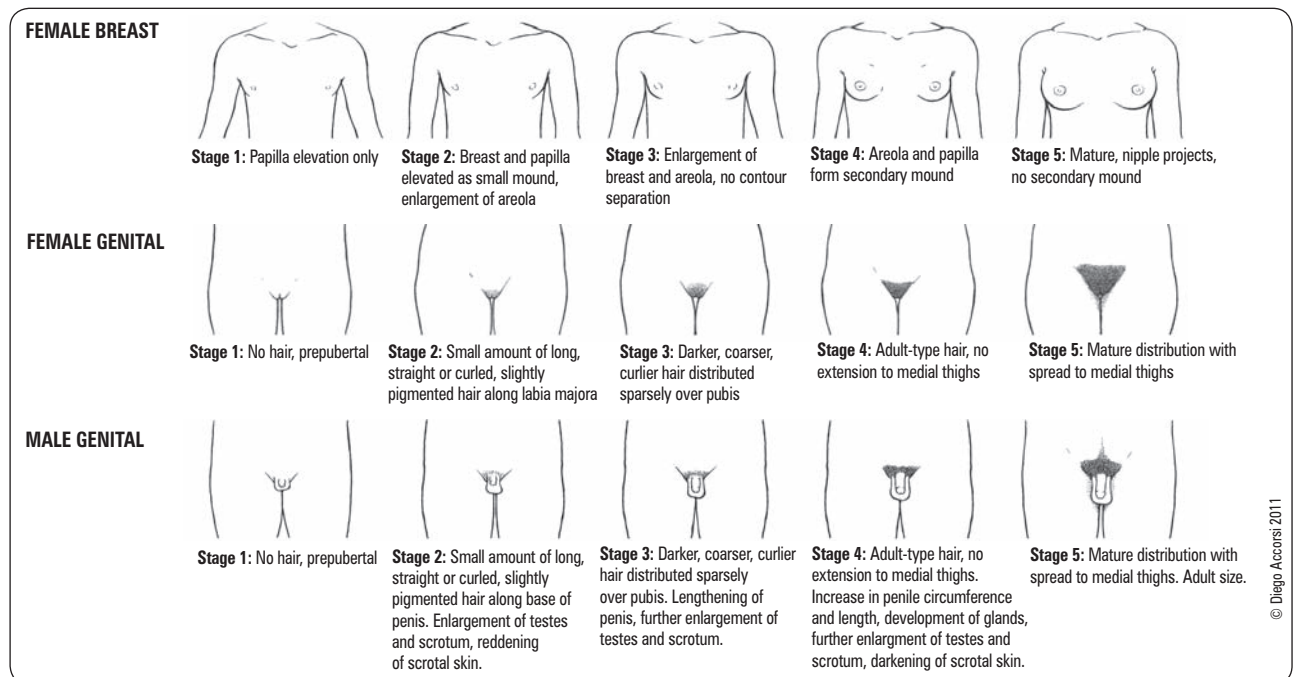


Figure 8. Tanner staging

## PRECOCIOUS PUBERTY

### Definition

- development of secondary sexual characteristics 2-2.5 SD before population mean
- <8 yr old for females, <9 yr old for males

### Epidemiology

- 1/10,000, F>M

### Etiology

- usually idiopathic in females (90%), more suggestive of pathology in males (50%)
- central (GnRH dependent)
  - hypergonadotropic hypergonadism; hormone levels as in normal puberty
  - premature activation of the HPG axis
  - differential diagnosis: idiopathic or constitutional (most common), CNS disturbances (tumours, hamartomas, post-meningitis, increased ICP, radiotherapy), neurofibromatosis (NF), primary severe hypothyroidism
- peripheral (GnRH independent)
  - hypogonadotropic hypergonadism
  - differential diagnosis: adrenal disorders (CAH, adrenal neoplasm), testicular/ovarian tumour, gonadotropin/hCG secreting tumour (hepatoblastoma, intracranial teratoma, germinoma), exogenous steroid administration, McCune-Albright syndrome, aromatase excess syndrome, rarely hypothyroidism (Van-Wyk-Grumbach syndrome)

**Clinical Presentation**

- history
  - symptoms of puberty, family history of precocious puberty, medical illness
- physical
  - growth velocity: prepubertal: 4 to 6 cm/yr, growth spurt: boys 8-10 cm/yr, girls 6-8 cm/yr
  - complete physical exam, including Tanner staging and neurological assessment
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, DHEA-S, 17-OH progesterone)
  - secondary tests: MRI head, pelvic U/S,  $\beta$ -hCG, GnRH and/or ACTH stimulation test



A child with proven central precocious puberty should receive an MRI of the brain.

**Management**

- indications for medical intervention to delay progression of puberty: rapid advancement of puberty, early age, risk of compromise of final adult height, psychological
- central causes: goals are to preserve height and alleviate psychosocial stress; GnRH agonists (e.g. leuprolide) most effective
- peripheral causes: goal is to limit effects of elevated sex steroids; treat underlying cause; medications that decrease the production of a specific sex steroid or blocks its effects (e.g. ketoconazole, spiroinolactone, tamoxifen, anastrozole), surgical intervention

**DELAYED PUBERTY****Definition**

- failure to develop secondary sex characteristics by 2-2.5 SD beyond the population mean
  - for males: lack of testicular enlargement by 14 yr old
  - for females: lack of breast development by 13 yr old OR absence of menarche by 16 yr old or within 5 yr of pubertal onset

**Epidemiology**

- M>F

**Etiology**

- usually constitutional delay in males, more suggestive of pathology in females
- central causes
  - constitutional delay in activation of hypothalamic-pituitary-gonadal axis (most common)
  - hypogonadotropic hypogonadism
- peripheral causes
  - hypergonadotropic hypogonadism (e.g. primary gonadal failure, gonadal damage, Turner syndrome, hormone deficiency, androgen insensitivity syndrome, etc.)

**Clinical Presentation**

- history
  - weight loss, short stature, family history of puberty onset, medical illness, high performance athletes (females)
- physical
  - growth velocity (minimum 4 cm/yr), Tanner staging, neurological exam, complete physical exam
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, IGF-1), CBC, electrolytes, BUN, Cr, liver function tests, liver enzymes, ESR, CRP, urinalysis
  - secondary tests: MRI head, pelvic U/S, karyotype, IBD panel, celiac disease panel, LH levels following GnRH agonist

**Management**

- identify and treat underlying cause
- hormonal replacement: cyclic estradiol and progesterone for females, testosterone for males

# Gastroenterology

## Vomiting

### History

- characteristic of emesis (e.g. projectile, bilious, bloody)
- pattern of emesis (e.g. association with feeds, cyclic, morning)
- associated symptoms (e.g. anorexia, diarrhea, etc.)
- red flags: bilious or bloody emesis, projectile vomit, abdominal distension and tenderness, high fever, signs of dehydration

### Physical Findings

- vital signs to determine clinical status and hydration state
- dictated by suspected differential (see Table 13)

### Investigations

- CBC, electrolytes, BUN, Cr, amylase, lipase done routinely
- in sick child, add: ESR, venous blood gases, culture and sensitivity (blood, stool), imaging
- dictated by suspected differential (see Table 13)

**Table 13. Common Differential Diagnosis, Associated Findings and Diagnostic Approach Based on Age**

Cause	Suggestive Findings	Diagnostic Approach
<b>NEONATES – NON-BILIOUS</b>		
Tracheoesophageal fistula	Vomiting, excessive secretions soon after birth (e.g. drooling, choking, respiratory distress), inability to feed, inability to advance through NG tube	Inability to advance NG tube, CXR, upper GI series with water-soluble contrast
Pyloric stenosis	Projectile vomiting immediately after feeding, dehydrated, palpable “olive” in RUQ, decreased stools, hunger	U/S of pylorus, upper GI study Electrolytes, blood gas (hypokalemic, hypochloremic metabolic alkalosis)
GERD	Fussiness after feeds, spit ups, arching of back, poor weight gain	Empiric trial of acid suppression, pH monitoring study, UGI, endoscopy
Sepsis	Fever, lethargy, tachycardia, tachypnea, widening pulse pressure	CBC, cultures (blood, urine, CSF), CXR
Inborn error of metabolism	Poor feeding, failure to thrive, jaundice, hepatosplenomegaly, cardiomyopathy, dysmorphism, developmental delay	Electrolytes, blood gas (hyponatremic, hyperkalemic metabolic acidosis), lactate, ammonia, LFTs, BUN, Cr, serum Glu, bilirubin, PT/PTT, CBC
<b>NEONATES – BILIOUS</b>		
Duodenal atresia	Bilious vomiting, abdominal distension, often seen in Down’s syndrome, jaundice, polyhydramnios during pregnancy	AXR, upper GI series (‘double bubble’ sign)
Malrotation with volvulus	Bilious emesis, abdominal distension, pain, bloody stool, shock	AXR, upper GI series, contrast enema
Hirschsprung’s disease	Bilious emesis, abdominal distension, pain, failure to pass stool	AXR, upper GI series, contrast enema, rectal biopsy
<b>CHILDREN AND ADOLESCENTS</b>		
Gastroenteritis	Diarrhea, fever, sick contact, recent travel	CBC, stool culture
Appendicitis	Periumbilical discomfort that later localizes to RLQ, fever, anorexia	Abdominal U/S
Intussusception	Colicky progressive abdominal pain, drawing of leg up to chest, lethargy, bloody stool	Abdominal U/S
Non-GI infection (e.g. meningitis)	Fever, localized findings depending on cause	Cultures (CSF, blood, urine), brain imaging
Increased intracranial pressure	Nocturnal waking, progressive recurrent headache worse with Valsalva, nuchal rigidity	Brain CT without contrast Therapeutic LP in idiopathic intracranial hypertension
Toxic ingestion	Finding possibly varying by substance- toxidrome, often a history of ingestion	Qualitative and sometimes quantitative levels (urine, blood)
Pregnancy	Amenorrhea, morning sickness, bloating, breast tenderness	Urine $\beta$ -HCG
Cyclic vomiting	At least 3 self-limited episodes of vomiting lasting 12 h, 7 d between episodes, no organic cause of vomiting	Diagnosis of exclusion



**Vomiting:** forceful expulsion of stomach contents through the mouth.

**Regurgitation:** the return of partially digested food from the stomach to the mouth.



### Pyloric Stenosis 3 Ps

Palpable mass  
Peristalsis visible  
Projectile vomiting (2-4 wk after birth)



**Management**

- rehydration (see *Nephrology*, P79)
- treat underlying cause (see detailed differential diagnosis above)

## Gastroesophageal Reflux

**Epidemiology**

- extremely common in infancy (up to 50%)

**Clinical Presentation**

- vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<30 mL)

**Investigations**

- thriving baby requires no investigation
- investigations required if concomitant FTT, feeding aversion, recurrent cough, pneumonia or bronchospasm, GI blood loss or symptoms persist after 18 mo

**Management**

- conservative: thickened feeds, frequent and smaller feeds
- medical:
  - short-term parenteral (NG) feeding to enhance weight gain
  - ranitidine, omeprazole: decreases gastric acidity, decreases esophageal irritation
  - domperidone, metoclopramide: improves gastric emptying and GI motility
- surgical: indicated for failure of medical therapy (Nissen fundoplication)

**Complications**

- esophagitis, strictures, Barrett's esophagus, FTT, aspiration, oral feeding aversion

## Tracheoesophageal Fistula (TEF)

- see [General Surgery](#), GS64



## Pyloric Stenosis

- see [General Surgery](#), GS61



## Duodenal Atresia

- see [General Surgery](#), GS63



## Malrotation of the Intestine

- see [General Surgery](#), GS62



## Diarrhea

- definition of diarrhea varies with diet and age (stool normalcy difficult to define in children)
- infants → increase in stool frequency to twice as often per day; older children → 3+ loose or watery stools/d
- duration: acute: <2 wk; chronic: >2 wk

**Pathophysiology**

- osmotic: due to non-absorbable solutes in GI tract (e.g. lactose intolerance)
- secretory: increased secretion of Cl<sup>-</sup> ions and water in intestinal lumen (e.g. bacterial toxin)
- malabsorption: decreased GI surface area (e.g. short bowel syndrome)

**History**

- frequency, duration, quality of diarrhea
- associated symptoms (e.g. fever, abdominal pain, hematochezia, etc.)
- recent antibiotic use or recent travel
- elements of diet

**Physical Findings**

- vital signs to determine clinical status and hydration state
- dictated by suspected differential (see Tables 14 and 15, P36)



Diarrhea is defined as an increase in frequency and/or decreased consistency of stools compared to normal.

Normal stool volume:  
Infants: 5-10 g/kg  
Children: 200 g/d



**Diarrhea Red Flags**  
Bloody stool, fever, petechiae or purpura, signs of severe dehydration, weight loss/FTT.

## Investigations

- acute diarrhea:
  - stool for culture and sensitivity, ova and parasites, electron microscopy for viruses, *C. difficile* toxin, microscopy (leukocytes suggestive of invading pathogen), blood and urine cultures, bloodwork
- chronic diarrhea:
  - serial heights, weights, growth percentiles
  - if child growing well and thriving, workup is limited (stool cultures as above, stool reducing substances)
  - red flags: poor growth, chronic rash, other serious infections, hospitalizations for dehydration
    - ♦ require full work-up (as per below)
  - stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, *C. difficile* toxin, 3 d fecal fat,  $\alpha$ -1 antitrypsin clearance, fecal elastase
  - urinalysis, urine culture
  - CBC, differential, ESR/CRP, smear, electrolytes, total protein, albumin, carotene,  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$ ,  $\text{Mg}^{2+}$ , Fe, ferritin, folate, fat-soluble vitamins, PTT, INR
  - sweat chloride, celiac screen, thyroid function tests, urine vanillyl mandelic acid (VMA) and homovanillic acid (HVA), HIV test, lead levels
  - CXR, upper GI series and follow-through
  - specialized tests: endoscopy, small bowel biopsy



### Indications for Medical Evaluation of Acute Diarrhea

- Age < 6 mo
- Fever
- Visible blood in stool
- Frequent, substantial volume of diarrhea
- Signs of dehydration
- Change in mental status

MMWR Recomm Rep 2003; 52 (RR-16):1-16

## Differential Diagnosis

Table 14. Differential Diagnosis of Diarrhea

	Infectious			Non-infectious
<b>Acute</b>	<b>Viral</b> Rotavirus Norwalk Enteric Adenovirus	<b>Bacterial</b> <i>Salmonella</i> <i>Campylobacter</i> <i>Shigella</i> Pathogenic <i>E. coli</i> <i>Yersinia</i> <i>C. difficile</i>	<b>Parasitic</b> <i>Giardia lamblia</i> <i>Entamoeba histolytica</i>	<b>Antibiotic-induced</b> Non-specific: associated with systemic infection Hirschsprung's disease Toxin ingestion Primary disaccharide deficiency
<b>Chronic</b>	<b>0 – 3 months</b>	<b>3 months – 3 years</b>	<b>3 – 18 years</b>	<b>Uncommon</b>
<b>ØFFT</b>	GI infection	GI infection Toddler's diarrhea	GI infection Lactase deficiency Irritable bowel syndrome	Drug-induced Chronic constipation UTI
<b>FFT</b>	Disaccharidase deficiency Cow's milk protein intolerance Cystic fibrosis	Celiac disease	IBD Endocrine (thyrotoxicosis, Addison's) Neoplastic (pheochromocytoma, lymphoma)	Short bowel syndrome Schwachman-Diamond syndrome

## Infective Diarrhea

Table 15. Infective Diarrhea

	Viral Infection	Bacterial Infection
<b>Etiology</b>	Most common cause of gastroenteritis Commonly: rotaviruses, astroviruses, Norwalk virus (typically older children)	
<b>Presentation Clinical</b>	Associated with URIs Resolves in 3-7 d Slight fever, malaise, vomiting, vague abdominal pain	Severe abdominal pain High fever Bloody diarrhea
<b>Risk Factors</b>	Day care	Travel Poorly cooked meat Poorly refrigerated foods Prolonged antibiotics
<b>Management</b>	Prevention and treatment of dehydration most important (see <i>Dehydration</i> , P79) Early refeeding advisable, start with small amounts of easily digested carbohydrates, postpone dairy and fibrous vegetables Antibiotic therapy when indicated, antidiarrheal medications not indicated Notify Public Health authorities if appropriate	

## Toddler's Diarrhea

### Epidemiology

- most common cause of chronic diarrhea during infancy
- onset between 6-36 mo of age, ceases spontaneously between 2-4 yr

### Clinical Presentation

- diagnosis of exclusion in thriving child
- 4-6 bowel movements per day
- diet history (e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption)
- stool may contain undigested food particles
- excoriated diaper rash

### Management

- reassurance that it is self-limiting
- 4Fs (adequate Fibre, normal Fluid intake, 35-40% Fat, discourage excess Fruit juice)

## Lactase Deficiency (Lactose Intolerance)

### Clinical Presentation

- chronic, watery diarrhea and abdominal pain, bloating associated with dairy intake
- primary lactose intolerance: crampy abdominal pain with loose stool (older children, usually of East Asian and African descent)
- secondary lactose intolerance: older infant, persistent diarrhea (post viral/bacterial infection, Celiac disease, or IBD)

### Diagnosis

- trial of lactose-free diet
- watery stool, acid pH, positive reducing sugars
- positive breath hydrogen test if >6 yr

### Management

- lactose-free diet, soy formula
- lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

## Irritable Bowel Syndrome

- diagnosis of exclusion in older child/adolescent; may be similar to recurrent abdominal pain
- management: encourage high fibre diet, reassurance, medications (cAMP inhibitors) rarely for refractory cases

## Celiac Disease

- see [Gastroenterology](#), G18
- in children: presents at any age, usually 6-24 mo with the introduction of gluten in the diet
- FTT with poor appetite, irritability, apathy, rickets, wasted muscles, flat buttocks, rarely distended abdomen
- GI symptoms: anorexia, nausea, vomiting, edema, anemia, abdominal pain
- non-GI manifestations: iron-deficiency anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty, behavioural changes
- associated with other autoimmune disorders



Celiac disease is associated with an increased prevalence of IgA deficiency. Since tTG is an IgA-detecting test, you must order an accompanying IgA level.



A Celiac disease diet must avoid gluten present in **"BROW"** foods

**B**arley  
**R**ye  
**O**ats (controversial)  
**W**heat

## Milk Protein Allergy

### Pathophysiology

- immune-mediated mucosal injury (IgE and non-IgE-mediated)

### Clinical Presentation

- up to 50% of children intolerant to cow's milk may be intolerant to soy protein as well
- often history of atopy
- can present as:
  - proctocolitis: mild diarrhea, small amounts of bloody stools (common presentation in young infant)
  - enterocolitis: vomiting, diarrhea, anemia, hematochezia
  - enteropathy: chronic diarrhea, hypoalbuminemia

**Management**

- casein hydrolysate formula (dairy-free e.g. Nutramigen®, Pregestimil®) or mother may remove all milk protein from diet and continue breastfeeding (with adequate calcium and vit D intake)

**Inflammatory Bowel Disease (IBD)**

- see [Gastroenterology](#), G19

**Cystic Fibrosis (CF)**

- see [Respirology](#), P95

**Constipation**

- decreased stool frequency (<3 stools/wk) and/or stool fluidity (hard, pellet-like)

**FUNCTIONAL CONSTIPATION**

- 99% of cases of constipation

**Pathophysiology**

- lack of fibre in diet or change in diet, poor fluid intake, behavioural
  - infants: often occurs when introducing cow's milk after breast milk due to high fat and solute content, lower water content
  - toddlers/older children: can occur during toilet training, or due to pain on defecation, stool withholding

**Management**

- clean out: PEG 3350 flakes, picosalax, biscodyl, PEGlyte®
- maintenance: adequate fluid intake (if <6 mo, 150 mL/kg/d), adequate dietary fibre, stool softening (PEG 3350, mineral oil), appropriate toilet training technique
- months of maintenance treatment is often required

**Complications**

- pain retention cycle: anal fissures + pain → withhold passing stool → chronic dilatation ± overflow incontinence

**HIRSCHSPRUNG'S DISEASE (Congenital Aganglionic Megacolon)**

- see [General Surgery](#), GS63

**OTHER ORGANIC DISORDERS CAUSING CONSTIPATION**

- endocrine: hypothyroidism, DM, hypercalcemia
- neurologic: spina bifida
- anatomic: bowel obstruction, anus (imperforate, atresia, stenosis)
- drugs: lead, chemotherapy, opioids

**Abdominal Pain****ACUTE ABDOMINAL PAIN****History**

- description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
- associated symptoms: nausea, vomiting, diarrhea, fever

**Physical Examination**

- abdominal exam, peritoneal signs, bowel sounds, rectal exam, rash

**Investigations**

- CBC, differential, urinalysis to rule out urinary tract infection (UTI)

**Table 16. Differential Diagnosis of Acute Abdominal Pain**

Gastrointestinal	Hepatobiliary Tract	Genitourinary	Hematologic	Miscellaneous
Gastroenteritis	Cholecystitis	UTI	Henoch-Schönlein Purpura	DKA
Appendicitis	Pancreatitis	Nephrolithiasis	Sickle cell crisis	Pneumonia
Meckel's diverticulum		Testicular torsion		Somatization
Mesenteric adenitis		Ovarian torsion		
Ileus		Ectopic pregnancy		
Intestinal obstruction (incarcerated hernia, intussusception, volvulus)		PID		
Malabsorption		Endometriosis		
IBS		Menstruation		
Constipation				

**APPENDICITIS**

- see [General Surgery](#), GS28
- most common cause of acute abdomen after 5 yr of age
- clinical features: low grade fever, abdominal pain, anorexia, N/V (after onset of pain), peritoneal signs (generalized peritonitis is a common presentation in infants/young children)
- treatment: surgical
- complications: perforation (common in young children), abscess

**INTUSSUSCEPTION**

- telescoping of segment of bowel into distal segment causing ischemia and necrosis

**Epidemiology**

- 90% idiopathic, children with CF or GJ tube at significantly increased risk
- 50% between 3-12 mo, 75% before 2 yr of age

**Pathophysiology**

- usual site: ileocecal junction; jejunum in children with GJ tubes
- lead point of telescoping segment may be swollen Peyer's patches, Meckel's diverticulum, polyp, malignancy, Henoch-Schönlein Purpura

**Clinical Presentation**

- "classic triad" (only in 10-15% of patients)
- sudden onset of recurrent, paroxysmal, severe periumbilical pain with pain-free intervals
- later vomiting (may be bilious) and rectal bleeding (late finding)
- shock and dehydration

**Intussusception – Classic Triad**

- Abdominal pain
- Palpable mass
- Red currant jelly stools

**Diagnosis**

- U/S, air enema

**Management**

- air enema can be therapeutic (reduces intussusceptions in 75% of cases), reduction under hydrostatic pressure, surgery rarely needed

**Chronic Abdominal Pain****Rule of 3s**

- 3 episodes of severe pain
- Child > 3 yr old
- Over 3 month period

**Red Flags for Organic Etiology of Chronic Abdominal Pain**

- Age < 5 yr old
- Fever
- Localizes pain away from midline
- Anemia
- Rectal bleeding
- Rash
- Pain awakens child at night
- Travel history
- Prominent vomiting, diarrhea
- Weight loss or failure to gain weight
- Joint pain

**Chronic Abdominal Pain****Epidemiology**

- prevalence: 10% of school children (peak at 8-10 yr), F>M

**Etiology**

- organic (<10%)
  - gastrointestinal
    - ♦ constipation (cause vs. effect), infectious
    - ♦ IBD, esophagitis, peptic ulcer disease, lactose intolerance
    - ♦ anatomic anomalies, masses
    - ♦ pancreatic, hepatobiliary
  - genitourinary causes
    - ♦ recurrent urinary tract infections, nephrolithiasis, chronic PID, Mittelschmerz
  - neoplastic
- Functional/Recurrent Abdominal Pain (RAP) (90%)

### Clinical Presentation

- clustering episodes of vague, crampy periumbilical/epigastric pain, vivid pain description
- seldom awakens child from sleep, less common on weekends
- aggravated by exercise, alleviated by rest
- psychological factors related to onset and/or maintenance of pain, school avoidance
- psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
- diagnosis of exclusion

### Investigations

- CBC, ESR, urinalysis, stools for O&P, C&S, occult blood

### Management

- continue to attend school
- manage any emotional or family problems, counselling
- trial of high fibre diet, trial of lactose-free diet
- reassurance

### Prognosis

- pain resolves in 30-50% of kids within 2-6 wk of diagnosis
- 30-50% of kids with RAP have functional pain as adults (e.g. irritable bowel syndrome)

## Abdominal Mass

Table 17. Differential Diagnosis for Abdominal Mass

	Benign	Malignant
<b>Renal</b> (note: 50% of abdominal masses in newborn are renal in origin)	Hydronephrosis Polycystic kidney disease (PCKD) Hamartoma	Nephroblastoma (Wilms' tumour) Renal cell carcinoma (RCC)
<b>Adrenal</b>		Neuroblastoma
<b>Ovarian</b>	Ovarian cysts	Ovarian tumours
<b>Other</b>	Splenomegaly Pyloric stenosis Abdominal hernia Teratoma Fecal impaction	Lymphoma Rhabdomyosarcoma Retroperitoneal sarcoma

## Upper Gastrointestinal Bleeding

- see [Gastroenterology](#), G25



## Lower Gastrointestinal Bleeding

- see [Gastroenterology](#), G27



### Epidemiology

- acute:
  - infectious (bacterial, parasitic)
  - antibiotic-induced (*C. difficile*)
  - necrotizing enterocolitis in preterm infants
  - anatomic
  - malrotation/volvulus, intussusception
  - Meckel's diverticulitis
  - anal fissures, hemorrhoids
  - vascular/hematologic
  - Henoch-Schönlein Purpura (HSP)
  - hemolytic uremic syndrome (HUS)
  - coagulopathy
- chronic:
  - anal fissures (most common)
  - colitis
  - inflammatory bowel disease (IBD)
  - allergic (milk protein)
  - structural
  - polyps (most are hamartomas)
  - neoplasms (rare)
  - coagulopathy

### Physical Examination

- hemodynamic status, evidence of FTT, fever
- anal and rectal exam: tags, fissures, anal fistulas, polyps, foreign body, blood per rectum
- stool appearance
- NG aspirate
- lower GI bleed may present as melena (if it involves the small bowel) or hematochezia



**Investigations**

- stool cultures (C&S, *C. difficile* toxin)
- urinalysis and microscopy
- CBC, smear, differential, ESR, CRP, electrolytes, urea, creatinine, INR, PTT, albumin, iron studies, amoeba titers
- radiologic investigations
- abdominal x-ray to rule out obstruction
- Meckel's radionuclide scan

**Management**

- acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
- once stable, endoscopy and/or surgery as indicated

## Genetics, Dysmorphisms and Metabolism

### Genetic Anomalies

**Minor and Major Anomalies**

- minor anomaly: an unusual anatomic feature that is of no serious medical or cosmetic consequence to the patient
- major anomaly: anomaly that creates significant medical, surgical or cosmetic problems for the patient

**Mechanism for Anomalies**

- malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
- disruption: results from the extrinsic breakdown of, or interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
- deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter deformation sequence)
- dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g. bone dysplasia)

**Multiple Anomalies**

- association: non-random occurrence of multiple independent anomalies that appear together more than would be predicted by chance but are not believed to have a single etiology (e.g. VACTERL)
- sequence: related anomalies that come from a single initial major anomaly or precipitating factor that changes the development of other surrounding or related tissues or structures (e.g. Potter sequence)
- syndrome: a pattern of anomalies that occur together and are caused by a single known or unknown cause (e.g. Down syndrome)

**VACTERL**

- V** Vertebral dysgenesis
- A** Anal atresia (imperforate anus)  
± fistula
- C** Cardiac anomalies
- T-E** TracheoEsophageal fistula  
± esophageal atresia
- R** Renal anomalies
- L** Limb anomalies

### Approach to the Dysmorphic Child

- genetic disorders are the most common cause of infant death in developed countries

**General Approach to the Dysmorphic Child**

- Are the anomalies major or minor?
- What is the mechanism underlying the anomaly?
- Do the anomalies fit as part of an association, sequence or syndrome?

**History**

- prenatal/obstetrical history (see [Obstetrics](#), OB2)
- complete 3 generation family pedigree: consanguinity, stillbirths, neonatal deaths, specific illnesses, intellectual disability, multiple miscarriages, ethnicity



## Physical Examination

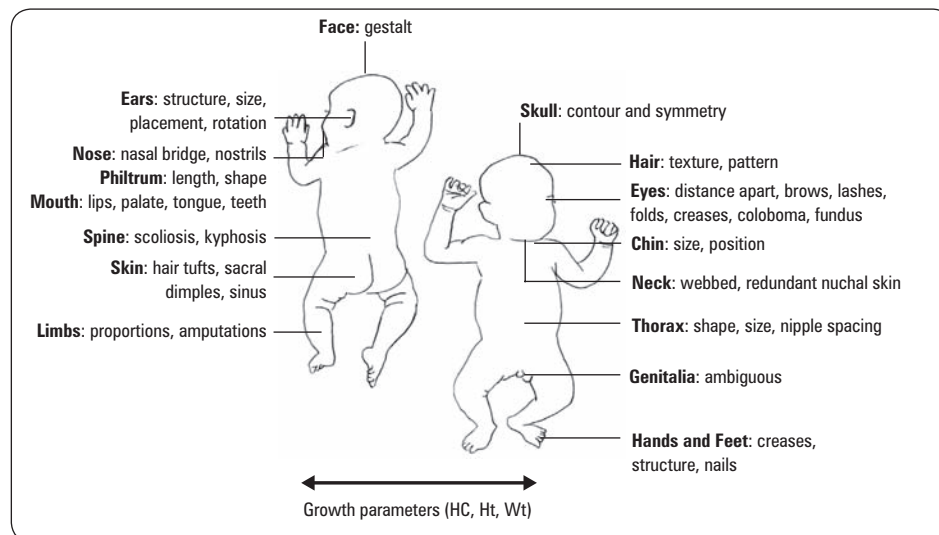


Figure 9. Physical examination of the dysmorphic child



Check the umbilical cord for 2 arteries and 1 vein. The presence of a single umbilical artery may be associated with other congenital anomalies.

## Investigations

- prenatal counselling and assessing risk of recurrence
- serial photographs if child is older
- x-rays for bony abnormalities
- cytogenetic studies
  - karyotype if recognized syndrome
  - chromosome microarray analysis (array comparative genomic hybridization) if developmental delay with multiple congenital anomalies
  - fluorescent in situ hybridization (FISH) if microdeletion syndrome or trisomy suspected
  - chromosomes in skin fibroblasts if mosaicism suspected and microarray is normal
- biochemistry: specific enzyme assays
- single gene testing

## Genetics

### MECHANISMS OF INHERITANCE

#### Mendelian Inheritance

- disorders caused by mutation of one or both copies of a gene, inherited in one of two patterns:
  - autosomal: encoded by genes on one of 22 pairs of autosomes (chromosomes 1-22)
  - X-linked: encoded by a gene on the X chromosome

#### Triplet Repeat Expansions

- disorder in which trinucleotide repeats in certain genes exceed the normal number and result in altered expression of the gene or production of an abnormal protein (e.g. Fragile X syndrome, spinocerebellar ataxias, myotonic dystrophy, Huntington disease)

#### Imprinting Disorders

- imprinting: epigenetic process that involves methylation or acetylation of DNA, affecting gene expression
- imprinted genes are expressed differently depending on whether they are inherited from the mother or the father (parent-of-origin gene expression)
- occur when imprinted alleles are silenced (e.g. Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome)

#### Mitochondrial Inheritance

- disorders caused by mutations of the DNA present in mitochondria
- inheritance pattern: mother passes on the defect to all her children; father does not pass on the defect since embryo only receives mitochondria from the mother (in the egg)

### METHODS OF GENETIC TESTING

- microarray analysis
  - a microarray is a collection of DNA probes attached to a solid surface
  - microarray analysis can identify small deletions or duplications of genetic material anywhere in the genome
  - indicated when there is developmental delay + one or more major malformations

#### Autosomal Dominant (AD)

Disorder is expressed in a heterozygote (inheritance is 'vertical', both males and females are affected and can transmit the trait) e.g. neurofibromatosis type I.

#### Autosomal Recessive (AR)

Disorder is manifested if both copies of the gene have mutations (inheritance is 'horizontal', disease not found in multiple generations, parents of an affected child are usually normal) e.g. cystic fibrosis.

#### X-linked

**Males** have a single X chromosome and are affected by recessive and dominant X-linked disorders, while **females** have two X chromosomes and recessive X-linked disorders are rarely expressed in females e.g. Duchenne Muscular Dystrophy (DMD).

- FISH
  - usually to identify a gain or loss of chromosomal material
- karyotype
  - microscopic analysis of all 46 chromosomes with a special stain that shows large changes in the number or structure of chromosomes

## Genetic Syndromes

**Table 18. Common Genetic Syndromes**

	Trisomy 21	Trisomy 18	Trisomy 13
<b>Disease</b>	Down syndrome	Edwards syndrome	Patau syndrome
<b>Incidence</b>	1:600-800 births Most common abnormality of autosomal chromosomes Rises with advanced maternal age from 1:1500 at age 20 to 1:20 by age 45	1:6000 live births Female:male = 3:1	1:10,000 live births
<b>Cranium/brain</b>	Mild microcephaly, flat occiput, 3rd fontanelle, brachycephaly	Microcephaly, prominent occiput	Microcephaly, sloping forehead, occipital scalp defect, holoprosencephaly
<b>Eyes</b>	Upslanting palpebral fissures, inner epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus	Microphthalmia, hypotelorism, iris coloboma, retinal anomalies	Microphthalmia, corneal abnormalities
<b>Ears</b>	Low-set, small, overfolded upper helix, frequent AOM, hearing loss	Low-set, malformed	Low-set, malformed
<b>Facial Features</b>	Protruding tongue, large cheeks, low flat nasal bridge, small nose	Cleft lip/palate Small mouth, micrognathia	60-80% cleft lip and palate
<b>Skeletal/MSK</b>	Short stature Excess nuchal skin Joint hyperflexibility (80%) including dysplastic hips, vertebral anomalies, atlantoaxial instability	Short stature Clenched fist with overlapping digits, hypoplastic nails, clinodactyly, polydactyly	Severe growth retardation Polydactyly, clenched hand
<b>Cardiac Defect</b>	50%, particularly AVSD	60% (VSD, PDA, ASD)	80% (VSD, PDA, ASD)
<b>GI</b>	Duodenal/esophageal/anal atresia, TE fistula, Hirschsprung's disease, chronic constipation	Hernia, TEF	
<b>GU</b>	Cryptorchidism, rarely fertile	Polycystic kidneys, cryptorchidism	Polycystic kidneys
<b>CNS</b>	Hypotonia at birth Low IQ, developmental delay, hearing problems Onset of Alzheimer's disease in 40s	Hypertonia	Hypo- or hypertonia Seizures, deafness Severe developmental delay
<b>Other Features</b>	Transverse palmar crease, clinodactyly and absent middle phalanx of the 5th finger 1% lifetime risk of leukemia Polycythemia Hypothyroidism	Small for gestational age (SGA) Rocker-bottom feet	Single umbilical artery Midline anomalies: scalp, pituitary, palate, heart, umbilicus, anus Rocker-bottom feet
<b>Prognosis/Management</b>	Prognosis: long-term management Per AAP Guidelines (Health Supervision of Children with Down syndrome), recommend chromosomal analysis, CBC, echo, yearly thyroid test, atlanto-occipital x-ray at 2 yr, sleep study, hearing test, and ophthalmology assessment	44% die in 1st month 10% survive past 1 yr (profound intellectual disability in survivors)	33% die in 1st month, 50% by 2nd month, 90% by 1 yr from FTT Profound intellectual disability in survivors

**Table 19. Most Common Sex Chromosome Disorders**

	Fragile X Syndrome	Klinefelter Syndrome	Turner Syndrome	Noonan Syndrome
<b>Genotype</b>	X-linked Genetic anticipation CGG trinucleotide repeat on X chromosome measurable by molecular analysis	47,XXY (most common) 48,XXXY, 49,XXXXY	45,X (most common)	46,XX or 46,XY Autosomal dominant (not a sex chromosome disorder) with variable expression Higher transmission of affected maternal gene
<b>Incidence</b>	1:3600 males, 1:6000 females Most common heritable cause of intellectual disability in boys	1:1000 live male births Increased risk with advanced maternal age	1:4000 live female births Risk not increased with advanced maternal age	1:2000 male and female live births
<b>Phenotype</b>	Overgrowth: Prominent jaw, forehead, and nasal bridge with long and thin face, large protuberant ears, macroorchidism, hyperextensibility, and high arched palate Complications: Seizures, scoliosis, mitral valve prolapse	Tall, slim, underweight No features prepuberty Postpuberty: male may suffer from developmental delay, long limbs, gynecomastia, lack of facial hair	Short stature, short webbed neck, low posterior hair line, wide carrying angle Broad chest, widely spaced nipples Lymphedema of hands and/or feet, cystic hygroma in newborn with polyhydramnios, lung hypoplasia Coarctation of aorta, bicuspid aortic valve Renal and cardiovascular abnormalities, increased risk of HTN Less severe spectrum with mosaic	Certain phenotypic features similar to females with Turner syndrome; therefore, sometimes called the "male Turner syndrome", although it affects both males and females Short stature, webbed neck, triangular facies, hypertelorism, low set ears, epicanthal folds, ptosis Pectus excavatum Right-sided congenital heart disease, pulmonary stenosis

Table 19. Most Common Sex Chromosome Disorders (continued)

	Fragile X Syndrome	Klinefelter Syndrome	Turner Syndrome	Noonan Syndrome
<b>IQ and Behaviour</b>	Mild to moderate intellectual disability, 20% of affected males have normal IQ ADHD and/or autism Female carriers may show intellectual impairment Male carriers may demonstrate tremor/ataxia syndrome in later life	Mild intellectual disability Behavioural or psychiatric disorders – anxiety, shyness, aggressive behaviour, antisocial acts	Mildly deficient to normal intelligence	Moderate intellectual disability in 25% of patients
<b>Gonad and Reproductive Function</b>	Prepubertal carrier females at risk of developing premature ovarian failure	Infertility due to hypogonadism/hypospermia	Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics	Delayed puberty
<b>Diagnosis/Prognosis/Management</b>	Molecular testing of <i>FMR1</i> gene: overamplification of the trinucleotide repeat, length of segment is proportional to severity of clinical phenotype (genetic anticipation)	Increased risk of germ cell tumours and breast cancer  Management: Testosterone in adolescence	Normal life expectancy if no complications Increased risk of X-linked diseases Management: ECHO, ECG to screen for cardiac malformation GH therapy for short stature Estrogen replacement at time of puberty for development of secondary sexual characteristics	Management: Affected males may require testosterone replacement therapy at puberty ECHO, ECG

Table 20. Other Genetic Syndromes

	DiGeorge Syndrome	Prader-Willi Syndrome	Angelman Syndrome	CHARGE Syndrome
<b>Genotype</b>	Microdeletions of chromosome region 22q11	Due to deletion of paternal chromosome 15q11 or two maternal chromosome 15s (maternal uniparental disomy)	Due to maternally derived deletion of the usually maternally expressed genes The paternal copy is silenced epigenetically	2/3 of children with CHARGE have been found to have a CHD7 mutation on chromosome 8
<b>Incidence</b>	Second most common genetic diagnosis (next to Down syndrome)	1:15,000		1:10,000
<b>Clinical Features</b>	<b>“CATCH 22”</b> Cyanotic CHD (may account for up to 5% of all cases of CHD) Anomalies: craniofacial anomalies typically micrognathia and low set ears Thymic hypoplasia “immunodeficiency” recurrent infections Cognitive impairment Hypoparathyroidism, hypocalcemia 22q11 microdeletions High risk for psychiatric disorders	<b>“H<sub>3</sub>O”</b> : Hypotonia and weakness, Hypogonadism, Obsessive Hyperphagia, Obesity Short stature, almond-shaped eyes, small hands and feet with tapering of fingers Development delay (variable) Hypopigmentation, DM II	Ataxia with severe intellectual disability, seizures, tremulousness, hypotonia Midface hypoplasia, fair hair, uncontrollable laughter	<b>“CHARGE”</b> <b>C</b> Coloboma <b>H</b> congenital Heart disease <b>A</b> choanal Atresia <b>R</b> mental Retardation <b>G</b> GU anomalies <b>E</b> Ear anomalies

## Muscular Dystrophy (MD)

- group of inherited diseases characterized by progressive skeletal and cardiac muscle degeneration

### DUCHENNE MUSCULAR DYSTROPHY (DMD)

#### Epidemiology

- 1:4000 males

#### Etiology

- X-linked recessive: 1/3 spontaneous mutations, 2/3 inherited mutations
- missing structural protein (dystrophin) → muscle fibre fragility → fibre breakdown → necrosis and regeneration

#### Clinical Presentation

- proximal muscle weakness by age 3, positive Gower's sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy



#### Gower's Sign

Child uses hands to “climb up” the legs to move from a sitting to a standing position.

**Diagnosis**

- molecular genetic studies of dystrophin gene (DMD) (first line)
- family history (pedigree analysis)
- increased CK (50-100x normal) and lactate dehydrogenase
- elevated transaminases
- muscle biopsy, electromyography (EMG)

**Management**

- supportive (e.g. physiotherapy, wheelchairs, braces), prevent obesity
- cardiac health monitoring and early intervention
- bone health monitoring and intervention (vit D, bisphosphonates)
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

**Complications**

- patient usually wheelchair-bound by 12 yr of age
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or CHF in 2nd-3rd decade

## Metabolic Disease

- an inherited disorder of metabolism; often autosomal recessive
- infants and older children may present with failure to thrive (FTT) or developmental delay
- in Ontario, universal newborn screening looks for: 9 organic acid disorders, 6 amino acid disorders, 5 fatty acid oxidation defects, 3 hemoglobinopathies, 2 endocrinopathies, galactosemia, biotinidase deficiency, cystic fibrosis, and hearing loss
- types of disorders
  - proteins: PKU, tyrosinemia, organic acid disorders, urea cycle defects
  - carbohydrates: galactosemia, glycogen storage diseases
  - fats: fatty acid oxidation defects
  - organelle disorders: congenital disorders of glycosylation, mucopolysaccharidosis

**Clinical Manifestations**

- vomiting and acidosis after feeding initiation (amino acid or carbohydrate metabolic disorder)
- hepatosplenomegaly (metabolites accumulate in the liver)
- neurologic syndrome: acute and chronic encephalopathy, intellectual disability, megalencephaly (mucopolysaccharide disorders)
- severe acidosis (aminoaciduria), hyperammonemia (urea cycle and organic acid disorders)
- growth retardation, seizures, coma, hypoglycemia
- autonomic manifestations (e.g. pallor, sweating, tremor)

**Physical Exam**

- odour: burnt sugar, sweaty feet, musty, ammonia-like
- skin: hypo/hyperpigmentation, rash, xanthomas
- hair: alopecia, hirsutism, abnormal architecture, fair colouring
- eyes: cornea (clouding, crystals), lens (cataracts, dislocation), retina (macular cherry red spot, pigment retinopathy, optic atrophy)

**Initial Investigations**

- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, ABGs (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects and glycogen storage diseases)
- lactate, ammonium (hyperammonemia with urea cycle defects), plasma  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$
- routine urinalysis: ketonuria must be investigated
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, plasma amino acid screen, urine organic acids, CSF glycine, free fatty acids (3- $\beta$ -hydroxybutyrate ratio  $>4$  in fatty acid oxidation defect)
- storage diseases: urine mucopolysaccharide and oligosaccharide screen



Metabolic disease must be ruled out in any newborn who becomes acutely ill after a period of normal behaviour and development or with a family history of early infant death even if the newborn screen is negative.

## Phenylketonuria (PKU)

### Epidemiology

- 1:10,000; autosomal recessive disease

### Etiology

- deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to build up of toxic metabolites
- mothers who have PKU may have infants with congenital abnormalities

### Clinical Presentation

- baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors, and mental retardation
- hypopigmentation due to low tyrosine (fair hair, blue eyes)

### Management

- PKU screening at birth
- dietary restriction of phenylalanine starting within the first 10 d of life
- duration of dietary restriction controversial – lifelong or until end of puberty; should be resumed during pregnancy to maintain normal phenylalanine levels

## Galactosemia

### Epidemiology

- 1:60,000; autosomal recessive disease

### Etiology

- most commonly due to deficiency of galactose-1-phosphate uridylyltransferase leading to an inability to process lactose/galactose

### Clinical Presentation

- signs of liver and renal failure, jaundice, FTT and cataracts with ingestion of lactose/galactose

### Management

- elimination of galactose from the diet (e.g. dairy, breast milk)
- most infants are fed a soy-based diet

### Complications

- increased risk of sepsis, especially *E. coli*
- if the diagnosis is not made at birth, liver and brain damage may become irreversible

## Hematology

### Approach to Anemia

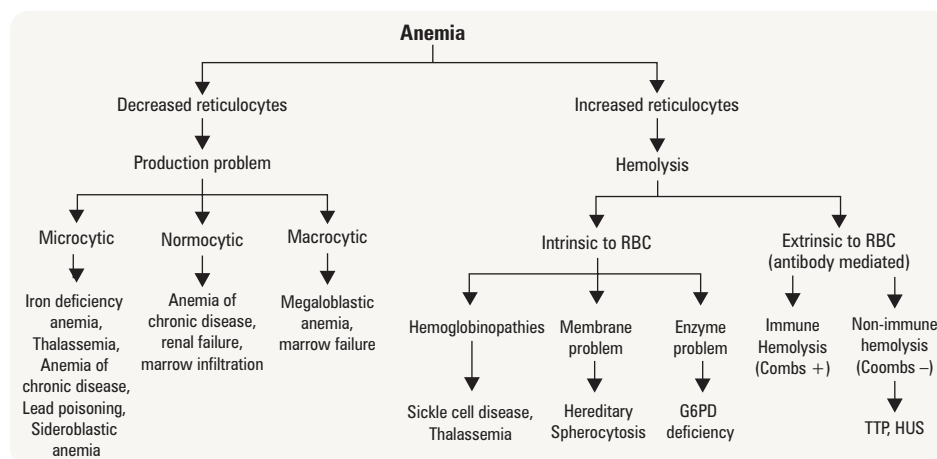


Figure 10. Anemia



## Physiologic Anemia

- high Hb (>170 g/L) and reticulocyte count at birth is caused by a hypoxic environment in utero
- after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 wk of life, there is virtually no erythropoiesis due to new O<sub>2</sub> rich environment), and increasing blood volume secondary to growth
- lowest levels about 100 g/L at 8-12 wk age (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
- no treatment usually required



### Normal Hb Values by Age

Age	Hb Range (g/L)
Newborn	137-201
2 wk	130-200
3 mo	95-145
6 mo-6 yr	105-140
7-12 yr	110-160
Adult female	120-160
Adult male	140-180

## Iron Deficiency Anemia

- most common cause of childhood anemia
- full term infants exhaust iron reserves by 6 mo of age
- premature infants have lower reserves, therefore exhausted by 2-3 mo of age
- common diagnosis between 6 mo-3 yr and 11-17 yr due to periods of rapid growth and increased iron requirements; adolescents also have poor diet and menstrual losses

### Etiology

- dietary risk factors
- age >6 mo: <2 servings/d of iron-fortified cereal, red meat, or legumes
- age <12 mo: use of low-iron formula (<10 mg/L), primary diet of cow, goat or soy milk
- age 1-5 yr: >20 oz/d of non-fortified milk
- blood loss
  - iatrogenic: repeated blood sampling (especially in hospitalized neonates)
  - allergic: cow's milk protein-induced colitis

### Clinical Manifestation

- usually asymptomatic until marked anemia, pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur

### Investigations

- CBC: low Hb, MCV and MCH, reticulocyte count normal or high (absolute number low)
- Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
  - ratio <13 suggests thalassemia; ratio >13 suggests iron deficiency
- blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikilocytosis
- iron studies: low ferritin, other (low iron, high TIBC)
- initial therapy: trial of iron

### Prevention

- breastfed term infants: begin iron supplementation (1 mg/kg/d) at 4-6 mo, continuing until able to eat ≥2 feeds/d of iron-rich foods
- non-breastfed (<50% of diet) term infants: give iron-fortified formula from birth
- premature infants: give iron supplements from 1 mo through to 1 yr of age
- no cow's milk until 9-12 mo, early introduction of red meat and iron-rich vegetables: total daily iron should be 11 mg (age 6-12 mo), 7 mg (age 1-3 yr)
- universal screening of Hb levels recommended at 9 mo
- children at risk (premature, LBW, low SES, First Nations, etc.) fed whole cow's milk in their first year

### Management

- encourage diverse, balanced diet, limit homogenized milk to 16-20 oz/d
- oral iron therapy: 6 mg/kg/d elemental iron, divided bid to tid, for 3 mo
  - increased reticulocyte count in 2-3 d (peaks day 5-7)
  - increased hemoglobin in 4-30 d
  - repletion of iron stores in 1-3 mo
  - repeat hemoglobin levels after 1 mo of treatment
- poor response to oral iron therapy: non-compliance, medication intolerance, ongoing blood loss, IBD, celiac disease, incorrect diagnosis

### Complications

- can cause irreversible effects on development if untreated (behavioural and intellectual deficiencies)
- angular cheilitis, glossitis, koilonychia (spoon nails)



MCV in childhood varies with age  
Rule of thumb: lower normal limit of  
MCV = 70 + age (yr) until 80 fl (adult  
standard).



Iron deficiency is rare in children  
<6 mo in the absence of blood loss or  
prematurity.



Ferritin is an acute phase reactant,  
therefore, normal or high ferritin does  
not exclude iron deficiency anemia  
during an infection.

## Anemia of Chronic Disease

- most often normocytic, normochromic (microcytic, hypochromic may occur with chronic infection/malignancy)
- multifactorial in origin
- chronic inflammatory states including juvenile idiopathic arthritis (JIA), chronic infections, chronic renal failure, and malignancies
- iron stores are variable and ferritin levels are unreliable (acute phase reactant); therefore bone marrow assessment may be necessary for diagnosis
- anemia of chronic renal failure predominantly caused by decreased erythropoietin (EPO) production; treat with EPO if necessary

## Sickle Cell Disease (SCD)

- see [Hematology](#), H19
- identification of specific genotypes important due to differences in frequency, type and severity of clinical complications (most severe: SS, less severe: SC, S- $\beta$  thalassemia, rare: SD)

### Epidemiology

- increased incidence in people of African and Mediterranean heritage

### Pathophysiology

- caused by a genetic defect at position 6 of the  $\beta$ -globin genes
  - HbS: single amino acid replacement (glutamic acid  $\rightarrow$  valine)
- RBCs sickle under conditions of stress (low pO<sub>2</sub>, dehydration, fever, acidosis)
- acute intravascular sickling results in infarction of tissue (capillary occlusion and thrombosis of spleen, lungs, bones, brain, digits)
- hemolysis causes chronic, well-compensated, normochromic normocytic anemia

### Presentation

- clinical disease presents at 5-6 mo of age after fall in fetal Hb
- anemia, fever (medical emergency – infection is leading cause of death in SCD), jaundice, splenomegaly, crisis (dactylitis is often the first presentation)
- sickle cell trait: asymptomatic (may have microscopic hematuria and later isothermia)

### Types of Crises

- vaso-occlusive crisis
  - due to obstruction of blood vessels by rigid, sickled cells  $\rightarrow$  tissue hypoxia  $\rightarrow$  cell death; presents as fever and pain in any organ; most commonly in long bones of arms and legs, chest, abdomen, CNS (stroke), dactylitis (in young children), priapism
  - acute chest crisis: fever, chest pain, progressive respiratory distress, increased WBC count, pulmonary infiltrates
- aplastic crisis: depression of erythropoiesis (decreased reticulocyte count to  $<1\%$ , decreased Hb), generally associated with infection (especially parvovirus B19)
- acute splenic sequestration: sudden, massive pooling of red cells in spleen, splenomegaly, tender spleen, acute fall in hemoglobin, shock, increased reticulocyte count

### Functional Asplenia

- splenic dysfunction usually by 5 yr of age secondary to auto-infarction
- susceptible to infection by encapsulated organisms (especially *S. pneumoniae*)
- all individuals with SCD should be on prophylactic antibiotics, and be vaccinated against pneumococcal/meningococcal/*H. influenzae* type b, along with hepatitis B and influenza
- febrile episodes require immediate evaluation: rule out bacteremia, meningitis, acute chest syndrome, and osteomyelitis (commonly due to *Salmonella* in SCD)

### Other Manifestations

- long term complications: growth delay, bony abnormalities (e.g. avascular necrosis (AVN) of femoral head), gallstones, retinopathy, restrictive lung disease (screen with PFTs), cardiomyopathy (screen with Echo), and pulmonary hypertension

### Management

- acute crises
  - admit for supportive and symptomatic treatment
  - fluids (1.5x maintenance; 1x maintenance only if in chest crisis), analgesia (opioid, multi-modal), antibiotics (e.g. 3rd generation cephalosporins), incentive spirometry and ambulation to decrease risk of chest crisis
  - straight transfusions for symptomatic/significant anemia, evolving chest crisis
  - RBC exchange transfusion for impending stroke, severe chest crisis, persistent priapism
  - O<sub>2</sub> if respiratory distress or chest crisis (with incentive spirometry)
  - cultures and CBC if febrile, reticulocyte counts, CXR or LP if indicated



8% of African Americans carry the HbS trait, 0.2% have the disease. Heterozygotes (trait) are relatively malaria-resistant.

- chronic
  - early aggressive treatment of infections, prophylactic antibiotics (daily oral penicillin)
  - pneumococcal, meningococcal, hepatitis B, Hib, and influenza vaccines
  - folate supplementation
  - hydroxyurea if frequent crises, history of acute chest syndrome (raises HbF level)
  - transcranial Doppler to assess risk of stroke
  - chronic transfusion program if history of stroke or abnormal transcranial Doppler
  - genetic counselling and education
  - annual fundoscopic exam (after 10 yr old)
  - bi-annual screening for pulmonary hypertension (after 12 yr old)
  - bi-annual chemistry and urinalysis to monitor organ dysfunction

## Thalassemia

- see [Hematology](#), H18



## Hereditary Spherocytosis

- see [Hematology](#), H21



## Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

- see [Hematology](#), H22



G6PD deficiency protects against parasitism of RBCs (i.e. malaria).



## Bleeding Disorders

- see [Hematology](#), H25

### Coagulation Defects

- bleeding into joints (hemarthroses) and muscles
- large spreading ecchymoses and hematomas

### Platelet Abnormalities

- petechiae, purpura, bruises, mucocutaneous bleeding (e.g. epistaxis, gingival bleeding), menorrhagia, prolonged bleeding from superficial cuts

**Table 21. Classification of Bleeding Disorders**

Site of Pathophysiology	Mechanism	Examples
Blood Vessels	Vasculitis	Henoch-Schönlein purpura
Platelets	Decreased production Increased destruction Increased consumption Dysfunctional	Drugs, marrow infiltration, leukemia/lymphoma Immune thrombocytopenic purpura, infection, drugs DIC, giant hemangioma, hypersplenism von Willebrand disease, drugs (ASA), uremia
Coagulation Pathway	Vitamin K deficiency Factor VIII deficiency Factor IX deficiency Abnormal vWF	Hemorrhagic disease of the newborn Hemophilia A Hemophilia B von Willebrand disease

## Immune Thrombocytopenic Purpura (ITP)

### Epidemiology

- most common cause of thrombocytopenia in childhood
- peak age: 2-6 yr, M=F
- incidence 5:100,000 children per year

### Etiology

- caused by autoantibodies that bind to platelet membranes → Fc-receptor mediated splenic uptake → destruction of platelets

## Clinical Presentation

- 50% present 1-3 wk after viral illness (URTI, chicken pox)
- sudden onset of petechiae, purpura, epistaxis in an otherwise well child
- clinically significant bleed in only 3% (severe bleed more likely with platelet count <10) with <0.5% risk of intracranial bleed
- no lymphadenopathy, no hepatosplenomegaly
- labs: thrombocytopenia with normal RBC, WBC
- bone marrow aspirate only if atypical presentation ( $\geq 1$  cell line abnormal, hepatosplenomegaly)
- differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), autoimmune (SLE, ALPS)

## Management

- observation vs. pharmacologic intervention highly debated; spontaneous recovery in >70% of cases within 3 mo
- treatment with IVIg or prednisone if mucosal or internal bleeding, platelets <10, or at-risk of significant bleeding (surgery, dental procedure, concomitant vasculitis or coagulopathy)
- life-threatening bleed: additional platelet transfusion  $\pm$  emergency splenectomy
- persistent (>3-12 mo) or chronic (>12 mo): re-evaluate; treat if symptoms persist
- supportive: avoid contact sports and ASA/NSAIDs

## Hemophilia

- see [Hematology](#), H29

## von Willebrand's Disease

- see [Hematology](#), H28

**Table 22. Evaluation of Abnormal Bruising/Bleeding**

	PFA	PT	PTT	VIII:C	vWF	Platelets	Fibrinogen
<b>Hemophilia A</b>	N	N	$\uparrow$	$\downarrow$	N	N	N
<b>Hemophilia B</b>	N	N	$\uparrow$	N	N	N	N
<b>von Willebrand disease</b>	$\uparrow$	N	N or $\uparrow$	$\downarrow$	$\downarrow$	N	N
<b>DIC</b>	N or $\uparrow$	$\uparrow$	$\uparrow$	$\downarrow$	N	$\downarrow$	$\downarrow$
<b>Vitamin K Deficiency</b>	N	$\uparrow$	$\uparrow$	N	N	N	N
<b>Thrombocytopenia</b>	$\uparrow$	N	N	N	N	$\downarrow$	N

BT = bleeding time; VIII:C = Factor VIII coagulant activity; vWF = von Willebrand's Factor; DIC = disseminated intravascular coagulation



### Corticosteroids versus Intravenous Immune Globulin for the Treatment of Acute Immune Thrombocytopenic Purpura in Children: A Systematic Review and Meta-analysis of Randomized Controlled Trials

*J Pediatr* 2005;147:521-527

**Study:** Meta-analysis of 10 RCTs from 1985-2003. RCTs compared corticosteroids and IVIg in the treatment of pediatric ITP, and had to include patient platelet counts.

**Patients:** 586 children 3 mo-18 yr of age who were presenting for the first time with primary acute ITP, with no other underlying condition.

**Intervention:** Corticosteroids and IVIg at any dose. Corticosteroid treatments included methylprednisolone 10-30 g/kg/d and prednisone 2-4 g/kg/d. IVIg dosing ranged from 0.5-1 g/kg/d. Treatment durations ranged from 1-5 d.

**Main Outcome:** Primary outcome was platelet levels  $>20,000/\text{mm}^3$  ( $20 \times 10^9/\text{L}$ ) at 48 h after treatment. (This outcome was chosen because intracranial hemorrhage rarely occurs at platelet above 20). Secondary outcomes included incidence of ICH.

**Results:** The relative risk (RR) of reaching a platelet count  $>20,000/\text{mm}^3$  at 48 h was 0.74 (95%CI 0.65-0.85) for corticosteroids versus IVIg (at any dose), with a NNT of 4.55 (95%CI 3.23-7.69). Subgroup analyses by dosing favoured IVIg in 6/10 dose comparisons. Only 3/586 children developed ICH – two were treated with corticosteroids and one with IVIg.

**Summary:** Children treated with corticosteroids are less likely to have a platelet count  $>20,000/\text{mm}^3$  than children treated with IVIg after 48 h of therapy. However, optimal dosing of IVIg is unclear, and impact of IVIg versus corticosteroids on ICH and mortality are unclear.



Extensive bruising in the absence of lab abnormalities: consider child abuse.

## Oncology

- cancer is the second most common cause of death after injuries in children after 1 yr of age
- cause is rarely known, but increased risk for:
  - chromosomal syndromes (e.g. Trisomy 21)
  - prior malignancy
  - neurocutaneous syndromes
  - immunodeficiency syndromes
  - family history
  - exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (40%), followed by brain tumours (20%), and lymphomas (15%)
- some malignancies are more prevalent in certain age groups
  - newborns: neuroblastoma, Wilms' tumour, retinoblastoma
  - infancy and childhood: leukemia, neuroblastoma, Wilms' tumour, retinoblastoma
  - adolescence: lymphoma, gonadal tumours, bone tumours
- unique treatment considerations in pediatrics because radiation, chemotherapy, and surgery can impact growth and development, endocrine function and fertility
- good prognosis: treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers (>80%)

## Leukemia

- see [Hematology](#), H35, H38, H41, H46



### Epidemiology

- mean age of diagnosis 2-5 yr but can occur at any age
- heterogeneous group of diseases:
  - acute lymphoblastic leukemia (ALL) (80%)
  - acute myeloblastic leukemia (AML) (15%)
  - chronic myelogenous leukemia (CML) (<5%)
- children with Down syndrome are 15x more likely to develop leukemia

### Clinical Presentation

- infiltration of leukemic cells into bone marrow results in bone pain, and bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in lymphadenopathy, hepatosplenomegaly, CNS manifestations, testicular disease
- fever, fatigue, weight loss, bruising, and easy bleeding

### Management

- combination chemotherapy using non-cross resistant chemotherapy agents

### Prognosis

- 80-90% 5-yr event-free survival for ALL, 50-60% 5-yr survival for AML
- patients are stratified into standard risk and high risk based on WBC and age; other prognostic factors include presence of CNS/testicular disease, immunophenotype, cytogenetics, and initial response to therapy (most important prognostic variable)

## Lymphoma

- see [Hematology](#), H42



### Epidemiology

- Hodgkin lymphoma: incidence is bimodal, peaks at ages 15-34 and >50 yr old
- Non-Hodgkin lymphoma: incidence peaks at 7-11 yr

### Clinical Presentation

- Hodgkin lymphoma:
  - most common presentation is persistent, painless, firm, cervical or supraclavicular lymphadenopathy
  - can present as persistent cough or dyspnea (secondary to mediastinal mass) or less commonly as splenomegaly, axillary or inguinal lymphadenopathy
  - constitutional symptoms (B symptoms) in 30% of children
- Non-Hodgkin lymphoma:
  - generally categorized into lymphoblastic, large cell, and Burkitt's/Burkitt's-like lymphoma
  - rapidly growing tumour with distant metastases (unlike adult non-Hodgkin lymphoma)
  - signs and symptoms related to disease site: most commonly abdomen, chest (mediastinal mass), head and neck region



'B Symptoms' = fever, night sweats, unexplained weight loss.

### Management

- Hodgkin lymphoma:
  - combination chemotherapy and radiation
  - aimed at limiting cumulative doses of anthracyclines (toxic to heart) and alkylators (risk of second malignancy, infertility) and limiting dose and field of radiation
  - increasing role for use of PET scanning to assess early disease response and plan therapy.
- Non-Hodgkin lymphoma:
  - combination chemotherapy
  - no added benefit of radiation in pediatric protocols.

### Prognosis

- Hodgkin lymphoma: >90% 5-yr survival
- Non-Hodgkin lymphoma: 75-90% 5-yr survival

## Brain Tumours

- see [Neurosurgery](#), NS10, NS38



## Wilms' Tumour (Nephroblastoma)

### Epidemiology

- usually diagnosed between 2-5 yr; M=F
  - most common primary renal neoplasm of childhood
  - 5-10% of cases both kidneys are affected (simultaneously or in sequence)

### Differential Diagnosis

- hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma

### Clinical Presentation

- 80% present with asymptomatic, unilateral abdominal mass
- may also present with hypertension, gross hematuria, abdominal pain, vomiting
- may have pulmonary metastases at time of diagnosis (respiratory symptoms)

### Associated Congenital Abnormalities

- WAGR syndrome (Wilms' tumour, Aniridia, Genital anomalies, mental Retardation) with 11p13 deletion
- Beckwith-Wiedemann syndrome
  - characterized by enlargement of body organs (especially tongue), hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
  - also at increased risk for developing hepatoblastoma, and less commonly adrenocortical tumours, neuroblastomas and rhabdomyosarcomas
- Denys-Drash syndrome
  - characterized by gonadal dysgenesis and nephropathy leading to renal failure

### Management

- staging ± nephrectomy
- chemotherapy; radiation for higher stages

### Prognosis

- 90% long-term survival

## Neuroblastoma

### Epidemiology

- most common cancer occurring in first year of life
- neural crest cell tumour arising from sympathetic tissues (neuroblasts)

### Clinical Presentation

- can originate from any site in sympathetic nervous system, presenting as mass in neck, chest or abdomen mass (most common site is adrenal gland)
- signs and symptoms of disease vary with location of tumour
  - thoracic: dyspnea, Horner's syndrome
  - abdomen: palpable mass
  - spinal cord compression
- metastases are common at presentation (>50% present with advanced stage disease)
  - usually to bone or bone marrow (presents as bone pain, limp)
  - can also present with periorbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, "blueberry muffin" skin nodules
- paraneoplastic: hypertension, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from vasoactive intestinal peptide secretion), opsomyoclonus
- diagnostic criteria (either of the following):
  - unequivocal histologic diagnosis from tumour tissue biopsy
  - evidence of metastasis to bone marrow ("rosettes") on aspirate analysis, with concomitant elevation of urine or serum catecholamine metabolite (VMA, HVA) levels

### Management

- depends on prognostic factors and may include combination of: surgery, radiation, chemotherapy, bone marrow transplantation

### Prognosis

- prognosis is often poor due to late detection
- good prognostic factors:
  - "age and stage" are important determinants of better outcome: 12-18 mo, stage I, II, IV-S disease ("S" designates a "Special" classification only pertaining to infants)
  - primary site: posterior mediastinum and neck
  - low serum ferritin
  - specific histology
  - tumour cell markers: aneuploidy, absent MYCN oncogene amplification



## Bone Tumours

- see [Orthopedics](#), OR42



## Febrile Neutropenia

- see [Infectious Diseases](#), ID39



## Tumour Lysis Syndrome

- see [Hematology](#), H50



## Hyperleukocytosis

- total WBC  $>100 \times 10^9/L$
- common presenting feature of leukemia
- medical emergency
- leukostasis = symptomatic hyperleukocytosis
  - presents clinically with respiratory or neurological distress caused by hyperviscosity of blood
  - risk of intracerebral hemorrhage, pulmonary leukostasis syndrome, tumour lysis syndrome
- management: fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes)

## Lymphadenopathy

### Clinical Presentations

- features of malignant lymphadenopathy (LAD): firm, discrete, non-tender, enlarging, immobile,  $\pm$  suspicious mass/imaging findings,  $\pm$  'B' symptoms
- fluctuance, warmth or tenderness are more suggestive of benign nodes (infection)



Most common cause of acute bilateral cervical LAD is viral illness.

### Differential Diagnosis

- infection:
  - viral: URTI, EBV, CMV, adenovirus, HIV
  - bacterial: *S. aureus*, GAS, anaerobes, *Mycobacterium* (e.g. TB), cat scratch disease (*Bartonella*)
  - other: fungal, protozoan, *Rickettsia*
- auto-immune: rheumatoid arthritis, SLE, serum sickness
- malignancy: lymphoma, leukemia, metastatic solid tumours
- storage diseases: Niemann-Pick, Gaucher's
- other: sarcoidosis, Kawasaki disease, histiocytoses

### Investigations

- generalized LAD
  - CBC and differential, blood culture
  - uric acid, LDH
  - ANA, RF, ESR
  - EBV/CMV/HIV serology
  - toxoplasma titre
  - fungal serology
  - CXR
  - TB tests
  - biopsy
- regional LAD
  - period of observation if asymptomatic
  - trial of oral antibiotics
  - ultrasound
  - biopsy (especially if persistent  $>6$  wk and/or 'B' symptoms)

# Infectious Diseases

## Fever

### Definition

- fever: no generally accepted definition, a practical definition is  $>38^{\circ}$  oral or rectal
- fever without a source/focus: acute febrile illness (typically  $<10$  d duration) with no cause of fever even after careful history and physical
- fever of unknown origin: daily or intermittent fevers for at least 2 consecutive weeks of uncertain cause after careful history and physical and initial laboratory assessment

### Etiology

- infectious: anatomic approach (CNS, ears, upper and lower respiratory tract, GI, GU, skin, soft tissue, bones and joints, etc.)
- inflammatory: mainly autoimmune (Kawasaki Disease, JIA, IBD, SLE, etc.)
- malignancy: childhood cancers (leukemia, lymphoma, neuroblastoma, etc.)
- miscellaneous: dehydration, drugs and toxins, post-immunization, familial dysautonomia, factitious disorder, etc.

### Diagnosis

- history: duration, height and pattern of fever, associated symptoms, exposures, constitutional symptoms, ethnic or genetic background, day care, sick contacts, travel
- physical: toxic vs. non-toxic, vitals, growth, complete exams of the: skin, HEENT, chest, abdomen, lymph nodes, genitalia
- investigations: guided by history, physical exam and clinical suspicion; see Figure 11 for guidelines for children from 0-3 yr old

### Evaluation of Neonates and Infants with Fever

- several protocols exist that attempt to identify neonates and young infants at low risk of serious bacterial infection (e.g. Rochester Criteria)
  - such protocols are not as sensitive in the 1-28 d age group; therefore, febrile neonates should be considered high risk regardless of clinical presentation and laboratory findings

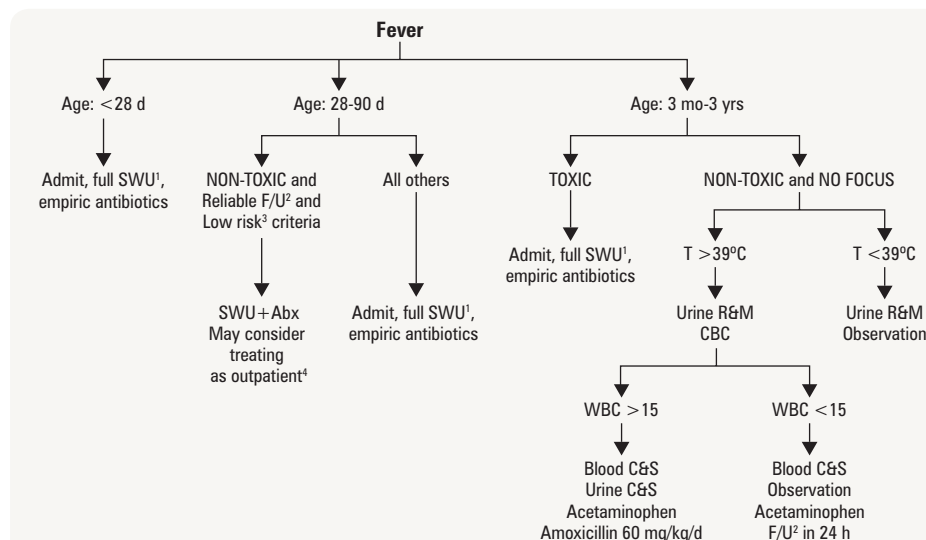
### Management

- admit to hospital if appropriate
- treat the source if known
- replace fluid losses (e.g. from vomiting, diarrhea, etc.); maintenance fluid needs are higher in febrile child
- reassure parents that most fevers are benign and self-limited
- antipyretics are not necessary in most cases, but can be given if child is uncomfortable (acetaminophen and/or ibuprofen)



**Rochester Criteria – developed to identify infants  $\leq 60$  d of age with fever at low risk of serious bacterial infection**

Clinically	Well
WBC count	$5-15 \times 10^9/L$
Bands	$<1.5 \times 10^9/L$
Urinalysis	10 WBC/HPF
Stool (if diarrhea)	5 WBC/HPF
Past Health	Born $>37$ wk Home with/before mom No hospitalizations No prior antibiotic use No prior treatment for unexplained hyperbilirubinemia No chronic disease



#### NOTES

- Full Septic Workup (SWU) – blood C&S, CBC and differential, urine R&M, C&S, LP, CXR if respiratory symptoms, stool C&S if GI symptoms
- Follow-up is crucial – if adequate F/U is not assured, a more aggressive diagnostic and therapeutic approach may be indicated
- Low-Risk (Rochester) Criteria
- Considerable practice variation exists in terms of empiric antibiotics treatment
- Important Principles – the younger the child, the greater the difficulty to clinically assess the degree of illness

Figure 11. Approach to the febrile child

## Acute Otitis Media (AOM)

### Definition

All of:

1. presence of middle ear effusion (MEE)
2. presence of middle ear inflammation (MEI)
3. acute onset of symptoms of MEE and MEI

### Epidemiology

- most frequent diagnosis in sick children visiting clinicians' offices and most common reason for antibiotic administration
- peak incidence between 6-15 mo; ~85% of children have >1 episode by 3 yr old
- seasonal variability: peaks in winter

### Etiology

- primary defect causing AOM: Eustachian tube dysfunction/obstruction → stasis/colonization by pathogens
- bacterial: *S. pneumoniae*, non-typable *H. influenzae*, *M. catarrhalis*, Group A *Streptococcus*, *S. aureus*
- viral: RSV, influenza, parainfluenza, adenovirus
- commonly due to bacterial/viral co-infection

### Risk Factors

- non-modifiable: young age, family history of OM, prematurity, orofacial abnormalities, immunodeficiencies, Down syndrome, race and ethnicity
- modifiable: lack of breastfeeding, day care attendance, household crowding, exposure to cigarette smoke and air pollution, pacifier use

### Diagnosis

- history
  - acute onset of otalgia or ear tugging in a preverbal child, otorrhea, decreased hearing
  - unexplained irritability, fever, upper respiratory symptoms, poor sleeping, anorexia, nausea, vomiting and diarrhea
- physical
  - febrile
  - MEE on otoscopy: immobile tympanic membrane, acute otorrhea, loss of bony landmarks, opacification of TM, air-fluid level behind TM
  - MEI on otoscopy: bulging TM with marked discolouration (hemorrhagic, red, grey, or yellow)

### Management

- observation for 48-72 h without antimicrobials may be appropriate since >80% of AOM in children resolve spontaneously
- criteria for watchful waiting approach:
  - child is >6 mo old
  - child does not have immunodeficiency, chronic cardiac or pulmonary disease, anatomical abnormalities of the head or neck, a history of complicated otitis media (suppurative complications of chronic perforation) or Down syndrome
  - the illness is not severe – otalgia appears to be mild and fever is <39°C in the absence of antipyretics
  - parents are capable of recognizing signs of worsening illness and can readily access medical care if the child does not improve
- antimicrobials are indicated if child does not meet the criteria for watchful waiting or does not improve/worsens during observation (Table 23)
- maintain hydration
- symptomatic relief: acetaminophen, ibuprofen
- referral to otolaryngology for myringotomy and tympanostomy tubes may be warranted for recurrent infections (see [Otolaryngology](#), OT39 for indications)

**Table 23. Treatment of AOM**

Antimicrobial Agents for Acute Otitis Media (AOM)
<b>First-line treatment (no penicillin allergy):</b> Amoxicillin: 75 mg/kg/d to 90 mg/kg/d divided three times per day
<b>Second-line treatment:</b> Cefprozil: 30 mg/kg/d divided twice per day Cefuroxime axetil: 30 mg/kg/d divided twice per day Ceftriaxone: 50 mg/kg intramuscularly (or intravenously) x 1 dose Azithromycin: 10 mg/kg OD x 1 dose, then 5 mg/kg OD x 4 doses Clarithromycin: 15 mg/kg/d divided twice per day
<b>If initial therapy fails (i.e. no symptomatic improvement after 2-3 d):</b> Amoxicillin-clavulanate: 90 mg/kg/d amoxicillin, 6.4 mg/kg/d clavulanate divided twice per day for 10 d If AOM-related symptoms do not resolve with amoxicillin/clavulanate, a course of ceftriaxone 50 mg/kg/d intramuscularly (or intravenously) once per day x 3 doses could be considered



#### Management of Acute Otitis Media

*Paediatr Child Health* 2009;14:457-460

**Purpose:** Updates a previous document published in 1998.

**Study:** Evidence-based guideline by the Canadian Pediatric Society (CPS).

**Recommendations:** The watchful waiting approach (observation for 48-72 h without antibiotics) is appropriate except for:

- Children ≤6 mo
- Children with immunodeficiency
- Children with chronic cardiac or pulmonary disease
- Children with anatomical abnormalities of the head or neck
- History of complicated otitis media
- Children with Down syndrome
- Parent are incapable of recognizing signs of worsening illness or cannot readily access medical care if child does not improve
- If the child's status worsens or fails to improve in 48-72 h, antibiotic treatment must be started.

**Complications**

- extracranial:
  - hearing loss and speech delay (secondary to persistent MEE), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
- intracranial:
  - meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis

## Diphtheria

**Definition**

- upper respiratory bacterial illness caused by *Corynebacterium diphtheriae*
- characterized by pharyngitis, low-grade fever, and nasopharyngeal pseudomembranes released by bacteria (with possible dermatologic, cardiac and/or nervous system involvement)

**Epidemiology**

- routine immunization has significantly reduced morbidity and mortality
- diphtheria now very rare

**Etiology**

- caused by lysogenized phage
- transmitted by direct contact or droplet spread; incubation period is 2-5 d

**Risk Factors**

- unvaccinated, immunocompromised, travel to or inhabitants of endemic countries

**History**

- early symptoms similar to a common cold: low-grade fever, sore throat, anorexia, malaise
- later symptoms (due to Diphtheria toxin): pallor, diaphoresis, stupor, coma

**Physical**

- grey membranes may cover tonsils and soft palate (at day 2-3); becomes greenish or black with hemorrhage
- cervical lymphadenopathy; "bull neck" secondary to submandibular edema in severe disease

**Investigations**

- throat culture (specifically state that diphtheria is suspected as some labs only look for group A *Streptococcus* on routine throat cultures)

**Management**

- treat based on clinical suspicion; awaiting culture results will postpone treatment and worsen prognosis
- diphtheria antitoxin
- penicillin G or erythromycin (halts further toxin production and prevents carrier state)

**Prognosis**

- 5-10 % mortality for respiratory diphtheria
- complications: airway obstruction, recurrent laryngeal nerve palsy
- associated conditions: diphtheritic peripheral neuritis, myocarditis

## Gastroenteritis

**Definition**

- inflammation (generally of infectious etiology) of the stomach and small intestine leading to illness characterized by nausea, vomiting and diarrhea

**Epidemiology**

- cause of 3-5 million childhood deaths annually worldwide
- viral gastroenteritis most commonly affects children aged 6 mo – 5 yr

**Etiology**

- viral (rotavirus, adenovirus, astrovirus), bacterial (*E. coli*, *Salmonella*, *Shigella*, *Campylobacter*) or parasitic (*Giardia lamblia*)
- rotavirus in ~50% of cases; primarily transmitted fecal-orally; incubation period of ~2 d
- antibiotic-associated (*Clostridium difficile*)

**Risk Factors**

- young age, day care attendance, infected household member, immunocompromised, antibiotic use (*Clostridium difficile*)

**History**

- non-specific: diarrhea, vomiting, fever, anorexia, headache, myalgias, abdominal cramps
- bacterial and parasitic agents more common in older children (2-4 yr): blood and/or mucous in stool, recent travel, consumption of unprocessed meats, recent antibiotic use or hospitalization
- recent infectious contacts: symptoms usually begin 24-48 h after exposure

**Physical**

- febrile
- dehydrated: must assess extent (see *Dehydration*, P79)

**Investigations**

- not usually necessary in young children
- stool analysis: leukocytes/erythrocytes suggests bacterial or parasitic etiology; pH <6 and presence of reducing substances suggests viral etiology

**Management**

- re-hydration: replace deficits, ongoing losses and maintenance needs (see P79)
- oral rehydration therapy (ORT) preferred for mild-moderate dehydration in acute gastroenteritis
- antiemetics may reduce vomiting, but increase diarrhea
- regular diet of small frequent feeds recommended in mild illness
- may return to age-appropriate diet once re-hydrated and vomiting stops
- antibiotics or antiparasitic agents sometimes indicated in bacterial or parasitic gastroenteritis
- promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission
- oral rotavirus vaccine now available in Canada

**Complications**

- viral gastroenteritis usually self-limiting (lasts 3-7 d in most cases)
- adverse effects related to hypovolemia, shock, tissue acidosis, and rapid onset and over-correction of electrolyte imbalances
- death in severe dehydration (rare in developed countries)

## HIV Infection

- see [Infectious Diseases](#), ID41

**Epidemiology**

- 20-30% risk of vertical transmission in untreated HIV infected women, <1% with antiretroviral treatment during pregnancy and perinatally

**Transmission**

- infants and children: most often vertical (transplacentally in majority, maternal blood, exposure to infected secretions during delivery, breast milk)
- adolescents: sexual intercourse, needles (IV drug use and tattoos), blood products (rare)

**Risk Factors**

- HIV positive mother or mother with HIV positive partner
- IV illicit drug use (IVDU)
- unprotected sex
- sexual abuse
- receipt of blood products (rare)

**Clinical Features of AIDS in Infants and Children**

- signs and symptoms occur often within the first year, most within 2 yr of age
- encephalopathy, recurrent/persistent thrush, persistent diaper candidiasis, chronic interstitial pneumonitis (relatively common), opportunistic infections (especially *Pneumocystis jiroveci* (PJP) pneumonia), hepatomegaly, lymphadenopathy, failure to thrive

**Management**

- adequate nutrition (breastfeeding contraindicated in developed countries)
- suppression of HIV with HAART
- prompt treatment of infections
- prophylaxis:
  - TMP/SMX for PJP, azithromycin for mycobacterium avium complex (MAC); nystatin, ketoconazole, acyclovir if indicated
  - all routine immunizations (including live vaccines if well), but avoid oral-polio vaccine and BCG

## Infectious Pediatric Exanthems

Disease	Pathogen(s)	Incubation period	Communicability	Mode of Transmission	Rash	Associated Features	Management	Outcomes and complications
<b>Erythema Infectiosum (aka Fifth Disease)</b>	Parvovirus B19	4-14 d	Low risk of transmission once symptomatic	Respiratory secretions or infected blood	Appearance: uniform, erythematous maculopapular 'lacy' rash Timing: 10-17 d after symptoms (immune response) Distribution: bilateral cheeks ('slapped cheeks') with circumoral sparing; may affect trunk and extremities	Initial 7-10 d of flu-like illness and fever Rash may be warm, non-tender, and pruritic Less common presentations include 'gloves and socks syndrome' or STAR complex (sore throat, arthritis, rash)	Supportive	Rash fades over days to week, but may reappear months later with sunlight, exercise Aplastic crisis
<b>Gianotti-Crosti Syndrome (aka Papular Acrodermatitis)</b>	EBV and Hep B (majority)	Variable	None	—	Appearance: asymptomatic symmetric papules Distribution: face, cheeks, extremities, spares trunk bilateral cheeks	Viral prodrome May have lymphadenopathy and/or hepatosplenomegaly	Supportive	Resolves in 3-12 wk
<b>Hand, Foot and Mouth Disease</b>	Coxsackie group A	3-5 d	Likely 1-7 d after symptoms but may be up to months	Direct and indirect contact with infected bodily fluids, fecal-oral	Appearance: vesicles and pustules on an erythematous base Distribution: acral	Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue)	Supportive	Mainly dehydration
<b>Herpes Simplex</b>	HSV 1,2	1-26 d	Direct contact, often through saliva for HSV-1 and sexual contact for HSV-2	Direct contact with infected secretions or mucuous membranes	Grouped vesicles on an erythematous base	Enanthem: vesicles/erosions in the ANTERIOR oral cavity (buccal mucosa, tongue) May present with herpetic whitlow (autoinoculation)	Mainly supportive Consider oral or topical antivirals	Local: secondary skin infections, keratitis, gingivostomatitis CNS: encephalitis Disseminated hepatitis, DIC
<b>Kawasaki Disease</b>	See P100							
<b>Measles</b>	Morbillivirus	8-13 d	4 d before and after rash	Airborne	Appearance: erythematous maculopapular Timing: 3 d after start of symptoms Distribution: starts at hairline and spreads downwards with sparing of palms and soles	Prodrome of cough, coryza, conjunctivitis (3 Cs) Enanthem: Koplik's spots 1-2 d before rash Desquamation Positive serology for measles IgM	Infected: symptomatic Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure Respiratory isolation, report to public health Prevention: MMR vaccine	Secondary bacterial infections: AOM, sinusitis, pneumonia Encephalitis Rare: myocarditis, pericarditis, thrombocytopenia, Stevens-Johnson syndrome, glomerulonephritis, subacute sclerosing panencephalitis



Disease	Pathogen(s)	Incubation period	Communicability	Mode of Transmission	Rash	Associated Features	Management	Outcomes and complications
<b>Non-Specific Enteroviral Exanthems</b>	Enteroviruses	Variable	Variable	Direct and indirect contact with infected bodily fluids	Polymorphous rash (macules, papules, vesicles, petechiae, utricaria)	Systemic involvement is rare, but possible	Supportive Diagnosis confirmed using viral cultures (NP and rectal swabs)	Self-limiting
<b>Rosela</b>	HHV 6	5-15 d	Unknown	—	Appearance: blanching, pink, maculopapular Timing: appears once fever subsides Distribution: starts at the neck and trunk and spreads to the face and extremities	High grade fever Common: irritability, anorexia lymphadenopathy, erythematous TM and pharynx, Nagayama sign Less common: cough, coryza, bulging fontanelles	Supportive	CNS: febrile seizures (10-25%), aseptic meningitis Thrombocytopenia
<b>Rubella</b>	Rubivirus	14-21 d	7 d before and after eruptions	Droplet	Appearance: pink, maculopapular Timing: 1-5 d after start of symptoms Distribution: starts on face and spreads to neck and trunk	Prodrome of low grade fever and occipital/retroauricular nodes STAR complex (sore throat, arthritis, rash) Positive serology for rubella IgM	Infected: symptomatic Prevention: MMR vaccine Report to public health	Excellent prognosis with acquired disease Arthritis may last days to weeks Encephalitis Irreversible defects in congenitally infected patients (i.e. congenital rubella syndrome)
<b>Scarlet Fever</b>	See P61							
<b>Varicella</b>	Varicella zoster virus	0-21 d	1-2 d pre-eruptions and 5 d post-eruption	Mainly airborne, but also through direct contact with vesicle fluid	Appearance: crops of skin lesions, polymorphic, from macules to papules to vesicles to crusts Timing: 1-3 d after start of symptoms Distribution: generalized	Significant pruritis Enanthem: vesicular lesions which may become pustular or ulcerate	Supportive Avoid salicylates (due to risk of Reye syndrome) Consider antivirals Respiratory and contact isolation, report to public health Prevention: varicella vaccine	Skin: bacterial suprainfection, necrotizing fasciitis CNS: acute encephalitis and cerebellar ataxia Systemic: hepatitis, DIC Congenital varicella syndrome if intrapartum infection

## Infectious Mononucleosis

### Definition

- systemic viral infection caused by Epstein-Barr virus (EBV) with multivisceral involvement; often called “the great imitator”

### Epidemiology

- peak incidence between 15-19 yr old
- ~50% of children in developed countries have a primary EBV infection by 5 yr old, but <10% of children develop clinical infection

### Etiology

- EBV: a member of herpesviridae
- transmission is mainly through infected saliva (“kissing disease”) and sexual activity (less commonly); incubation period of 1-2 mo

### Risk Factors

- infectious contacts, sexually active, multiple sexual partners in the past

### History

- prodrome: 2-3 d of malaise, anorexia
- infants and young children: often asymptomatic or mild disease
- older children and adolescents: malaise, fatigue, fever, sore throat, abdominal pain (often LUQ), headache, myalgia

### Physical

- classic triad: febrile, generalized non-tender lymphadenopathy, pharyngitis/tonsillitis (exudative)
- ± hepatosplenomegaly
- ± periorbital edema, ± rash (urticarial, maculopapular or petichial) – more common after inappropriate treatment with  $\beta$  lactam antibiotics
- any “-itis” (including arthritis, hepatitis, nephritis, myocarditis, meningitis, encephalitis, etc.)

### Investigations

- heterophil antibody test (Monospot® test)
  - 85% sensitive in adults and older children, but only 50% sensitive if <4 yr of age
  - false positive results with HIV, SLE, lymphoma, rubella, parvovirus
- EBV titres
- CBC and differential, blood smear: atypical lymphocytes, lymphocytosis, Downey cells, ± anemia, ± thrombocytopenia
- throat culture to rule out streptococcal pharyngitis

### Management

- supportive: adequate rest, hydration, saline gargles and analgesics for sore throat
- splenic enlargement is often not clinically apparent so all patients should avoid contact sports for 6-8 wk
- if airway obstruction secondary to nodal and/or tonsillar enlargement is present (especially younger children), admit for steroid therapy
- acyclovir does NOT reduce duration of symptoms or result in earlier return to school/work

### Prognosis

- most acute symptoms resolve in 1-2 wk, though fatigue may last for months
- short-term complications: splenic rupture, Guillain-Barré syndrome

## Infectious Pharyngitis/Tonsillitis

### Definition

- inflammation of the pharynx, especially the tonsils if present, causing a sore throat

### Etiology

- viral (~80%): adenoviruses, enteroviruses, coxsackie, upper respiratory tract viruses, EBV, CMV
- bacterial (~20%): mainly Group A *Streptococcus*, *M. pneumonia* (older children), *N. gonorrhea* (sexually active), *C. diphtheriae* (unvaccinated)
- fungal: *Candida*

### Epidemiology

- season: GAS pharyngitis more common in late winter or early spring; viral all yr long
- age: GAS pharyngitis peak incidence at 5-12 yr of age and uncommon <3 yr; viral pharyngitis affects all ages

## History

- GAS: sore throat (may be severe), fever, malaise, headache, abdominal pain, N/V, absence of other URTI symptoms
- viral: sore throat (often mild), conjunctivitis, cough, rhinorrhea, hoarseness, diarrhea, flu-like symptoms (fever, malaise, myalgias)

## Physical

- GAS: febrile, pharyngeal/tonsillar erythema and exudates, enlarged (>1 cm) and tender anterior cervical lymph nodes, palatal petechiae, strawberry tongue, scarlatiniform rash
- viral: afebrile, absent/mild tonsillar exudates, minor and non-tender adenopathy, viral exanthems

## Investigations

- no single sign or symptom reliably identifies GAS as the causative organism in children with sore throat
- scores are used to predict if throat culture will be positive (e.g. McIsaac Criteria)
  - these score systems have not been found to be sensitive or specific enough to diagnose GAS in children and adolescents with sore throat
- suspected diagnosis of GAS pharyngitis should be confirmed with a rapid streptococcal antigen test and a follow-up throat culture if the rapid test is negative

## Management

- antibiotics (for group A *Streptococcus/S. pyogenes*)
  - penicillin V or amoxicillin or erythromycin (if penicillin allergy) x 10 d
  - can prevent rheumatic fever if given within 9 d of symptoms; does NOT alter risk of post-streptococcal glomerulonephritis
- supportive: hydration and acetaminophen for discomfort due to pain and/or fever
- follow-up: if uncomplicated course, no follow-up or post-antibiotic throat cultures needed
- prophylaxis: consider tonsillectomy for proven, recurrent streptococcal tonsillitis

## Complications

- preventable with antibiotics: AOM, sinusitis, cervical adenitis, mastoiditis, retropharyngeal/peritonsillar abscess, sepsis
- immune-mediated complications: scarlet fever, acute rheumatic fever, post-streptococcal glomerulonephritis, reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A *Streptococci* (PANDAS)

## SCARLET FEVER

- diffuse erythematous eruption
- delayed-type hypersensitivity reaction to pyrogenic exotoxin produced by Group A *Streptococcus*
- acute onset of fever, sore throat, strawberry tongue
- 24-48 h after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa; Pastia's lines may be present
- within 24 h, sandpaper rash becomes generalized with perioral sparing, non-pruritic, non-painful, blanchable
- rash fades after 3-4 d, may be followed by desquamation
- treatment is penicillin, amoxicillin, or erythromycin x 10 d

## RHEUMATIC FEVER

- inflammatory disease due to antibody cross-reactivity following GAS infection
- affects ~1:10,000 children in developed world; much more prevalent in developing nations; peak incidence at 5-15 yr of age
- mainly a clinical diagnosis based on Jones Criteria (revised)
  - requires 2 major OR 1 major and 2 minor (see sidebar) PLUS evidence of preceding strep infection [history of scarlet fever, group A streptococcal pharyngitis culture, positive rapid Ag detection test, anti-streptolysin O titers (ASOT)]
- treatment
  - penicillin or erythromycin for acute course x 10 d
  - prednisone if severe carditis
- secondary prophylaxis with daily penicillin or erythromycin
- complications:
  - acute: myocarditis, conduction system aberrations (sinus tachycardia, atrial fibrillation), valvulitis (acute MR), pericarditis
  - chronic: valvular heart disease (mitral and/or aortic insufficiency/stenosis), infectious endocarditis ± thromboembolic phenomenon
  - onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever



### McIsaac Criteria (if >3 yr old)

#### HOT LACE

**Hot** – Fever >38° C

**Lymphadenopathy**: anterior, tender, cervical

**Age** 3-14 yr

**No Cough**

**Erythematous**, exudative tonsils

CMAJ 1998;158(1):75-83



### Scarlet Fever

#### 4 Ss and 4 Ps

**Sore throat**

**Swollen tonsils**

**Strawberry tongue**

**Sandpaper rash**

**Perioral Sparing**

**Non-Pruritic**

**Non-Painful**

**Peeling**



### Jones Criteria

#### Major: STREP

Sydenhams chorea

Transient migratory arthritis

Rheumatic subcutaneous nodules

Erythema marginatum

Pancarditis (endocarditis, myocarditis, pericarditis)

#### Minor: PEACE

PR interval prolonged

ESR elevated

Arthralgias

CRP elevated

Elevated temperature (fever)

**POST-STREPTOCOCCAL GLOMERULONEPHRITIS**

- glomerular immune complex disease following primary GAS infection of pharynx or skin
- most common in children aged 4-8 yr old; M>F
- antigen-antibody mediated complement activation with diffuse, proliferative glomerulonephritis
- occurs 1-3 wk following initial GAS infection (skin or throat)
- clinical presentation varies from asymptomatic, microscopic and macroscopic (cola coloured urine) hematuria to all features of nephritic syndrome (see P82)
- diagnosis is confirmed with elevated serum antibody titres against streptococcal antigens (ASOT, anti-DNaseB), low serum complement (C3)
- management:
  - symptomatic: fluid and sodium restrictions; loop diuretics for hypertension and edema
  - in severe cases, may require dialysis if renal function significantly impaired
  - treat with penicillin or erythromycin if evidence of persistent GAS infection
- 95% of children recover completely within 1-2 wk; 5-10% have persistent hematuria

## Meningitis

**Definition**

- inflammation of the meninges surrounding the brain and spinal cord

**Epidemiology**

- peak age: 6-12 mo; 90% of cases occur in children <5 yr old

**Etiology**

- viral: enteroviruses, herpes simplex virus (HSV)
- bacterial: age-related variation in specific pathogens (see Table 25)
- fungal and parasitic meningitis also possible
- most often due to hematogenous spread or direct extension from a contiguous site

**Risk Factors**

- unvaccinated
- immunocompromised: asplenia, diabetes mellitus, HIV, prematurity
- recent or current infections: AOM, sinusitis, orbital cellulitis,
- neuroanatomical: congenital defects, dermal sinus, neurosurgery, cochlear implants, recent head trauma
- exposures: day care centres, household contact, recent travel

**History**

- signs and symptoms variable and dependent on age, duration of illness and host response to infection
- infants: fever, lethargy, irritability, poor feeding, vomiting, diarrhea, respiratory distress, seizures
- children: fever, headache, photophobia, N/V, confusion, back/neck pain/stiffness, lethargy, irritability

**Physical**

- infants: toxic, hypothermia, bulging anterior fontanelle, respiratory distress, apnea, petechial/purpuric rash, jaundice, omphalitis
- children: toxic, ↓ LOC, nuchal rigidity, Kernig's and Brudzinski's signs, focal neurologic findings, petechial/purpuric rash

**Investigations**

- blood work: CBC, electrolytes, Cr, BUN, glucose, culture with sensitivity
- lumbar puncture required for definitive diagnosis
  - Gram stain, bacterial culture and sensitivity, WBC count and differential, RBC count, glucose, protein concentration (Table 24)
  - acid-fast stain if suspect TB
  - latex agglutination tests or PCR for specific bacteria if available (helpful if already treated with antibiotics)
  - CSF cloudy in bacterial meningitis
  - urinalysis and urine C&S in infants, Gram stain and culture of petechial/purpuric lesions

**Signs of Meningismus**

**BONK on the head**  
Brudzinski's sign  
Opisthotonos\*  
Nuchal rigidity  
Kernig's sign

\*Opisthotonos: rigid spasm of the body, with the back fully arched and the heels and head bent back

**Table 24. CSF Findings of Meningitis**

Component	Normal Child	Normal Newborn	Bacterial Meningitis	Viral Meningitis	Herpes Meningitis
WBC (/μL)	0-6	0-30	>1000	100-500*	10-1000
Neutrophils (%)	0	2-3	>50	<40	<50
Glucose (mg/dL)	40-80	32-121	<30	>30	>30
Protein (mg/dL)	20-30	19-149	>100	50-100	>75
RBC (/μL)	0-2	0-2	0-10	0-2	10-50

\*Lymphocytes predominate Modified from Peds in Review 1993;14:11-18 and Ped Inf Dis J 1996;15:298-303

### Management

- supportive care
  - preservation of adequate cerebral perfusion by maintaining normal BP and managing ↑ ICP
  - close monitoring of fluids, electrolytes, glucose, acid-base disturbances, coagulopathies
- bacterial meningitis
  - if suspected or cannot be excluded, commence empiric antibiotic therapy while awaiting cultures or if LP contraindicated or delayed
  - adjuvant dexamethasone BEFORE antibiotic for Hib meningitis; consider for those >6 wk with pneumococcal meningitis
  - isolation with appropriate infection control procedures until 24 h after culture-sensitive antibiotic therapy
  - fluid restrict if any concern for SIADH
  - hearing test
  - report to public health; prophylactic antibiotics for close contacts of Hib and *N. meningitidis* meningitis

**Table 25. Antibiotic Management of Bacterial Meningitis**

Age	Main pathogens	Antibiotics
0 to 28 d	GBS, <i>E. coli</i> , <i>Listeria</i> Other: Gram-negative bacilli	Ampicillin + cefotaxime
28 to 90 d	Overlap of neonatal pathogens and those seen in older children	Ampicillin + cefotaxime ± vancomycin
>90 d	<i>S. pneumoniae</i> , <i>N. meningitidis</i>	Ceftriaxone ± vancomycin

- viral meningitis
  - mainly supportive (except for HSV)
  - acyclovir for HSV meningitis
  - report to public health
- prophylaxis: appropriate vaccinations significantly decrease incidence of bacterial meningitis (see *Routine Immunization*, P3)

### Complications

- mortality: neonate 15-20%, children 4-8%; pneumococcus > meningococcus > Hib
- acute: SIADH, subdural effusion/empyema, brain abscess, disseminated infection (osteomyelitis, septic arthritis, abscess), shock/DIC
- chronic: hearing loss, neuromotor/cognitive delay, learning disabilities, neurological deficit, seizure disorder, hydrocephalus

## Mumps

### Definition

- acute, self-limited viral infection that is most commonly characterized by adenitis, and swelling of the parotid glands

### Epidemiology

- incidence in Ontario has declined since introduction of two-dose MMR vaccination schedule
- average of 25 reported cases per year
- majority of reported cases in children between 5-10 yr of age

### Etiology

- Mumps virus (RNA virus of the genus *Rubulavirus* in the *Paramyxoviridae* family)
- transmission via respiratory droplets, direct contact, fomites
- incubation period: 14-25 d
- infectivity period: 7 d pre-parotitis-5 d post-parotitis
- upper respiratory tract → lymph nodes → salivary glands, gonads, pancreas, meninges, kidney, heart, thyroid

**History**

- non-specific prodrome of fever, headache, malaise, myalgias (especially neck pain)
- usually followed within 48 h by parotid swelling secondary to parotitis (bilateral, preauricular, ear pushed up and out)
- parotid gland is tender and pain worsened with spicy or sour foods
- one third of infections do not cause clinically apparent salivary gland swelling and may simply present as an URTI

**Investigations**

- clinical diagnosis, but may be confirmed with IgM positive serology within 4 wk of acute infection
  - may also use PCR or viral cultures from oral secretions, urine, blood, and CSF
  - blood work: CBC (leukopenia with relative lymphocytosis), serum amylase (elevated)

**Management**

- mainly supportive: analgesics, antipyretics, warm or cold packs to parotid may be soothing
- admit to hospital if serious complications (meningitis, pancreatitis)
- droplet precautions recommended until 5 d after onset of parotid swelling
- prophylaxis: routine vaccination (see *Routine Immunization*, P3)

**Complications**

- common: aseptic meningitis, orchitis/oophoritis
- less common: encephalitis, pancreatitis, thyroiditis, myocarditis, arthritis, glomerulonephritis, ocular complications, hearing impairment

## Pertussis

**Definition**

- prolonged respiratory illness characterized by paroxysmal coughing and inspiratory “whoop”

**Epidemiology**

- ~10 million children <1 yr old affected worldwide, causes up to 400,000 deaths per year
- greatest incidence among children <1 yr (not fully immunized) and adolescents (waning immunity)

**Etiology**

- *Bordetella pertussis*: Gram negative pleomorphic rod
- highly contagious; transmitted via respiratory droplets released during intense coughing
- incubation period: 6-20 d; most contagious during catarrhal phase but may remain contagious for weeks after

**History**

- prodromal catarrhal stage
  - lasts 1-7 d; URTI symptoms (coryza, mild cough, sneezing) with NO or LOW-GRADE fever
- paroxysmal stage
  - lasts 4-6 wk; characterized by paroxysms of cough (“100 day cough”), sometimes followed by inspiratory whoop (“whooping cough”)
  - infants <6 mo may present with post-tussive apnea, whoop is often absent
  - onset of attacks precipitated by yawning, sneezing, eating, physical exertion
  - ± post-tussive emesis, may become cyanotic before whoop
- convalescent stage
  - lasts 1-2 wk; characterized by occasional paroxysms of cough, but decreased frequency and severity
  - non-infectious but cough may last up to 6 mo

**Investigations**

- nasopharyngeal (NP) specimen using aspirate or NP swab
  - gold standard: culture using special media (Regan-Lowe agar)
  - PCR to detect pertussis antigens
- blood work: CBC (lymphocytosis) and serology (antibodies against *B. pertussis*)

**Management**

- admit if paroxysms of cough are associated with cyanosis and/or apnea and give O<sub>2</sub>
- supportive care
- antimicrobial therapy indicated if *B. pertussis* isolated, or symptoms present for <21 d
  - use macrolide antibiotics (azithromycin, erythromycin or clarithromycin)
- droplet isolation until 5 d of treatment
  - report to public health



- prophylaxis
  - macrolide antibiotics for all household contacts
  - prevention with vaccination in infants and children (Pentacel®), and booster in adolescents (Adacel®) (see *Routine Immunization*, P3)

### Complications

- pressure related from paroxysms: subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
- respiratory: sinusitis, pneumonia, aspiration, atelectasis, pneumomediastinum, pneumothorax, alveolar rupture
- neurological: seizures (~3%), encephalopathy, intracranial hemorrhage
- mortality: ~0.3%; highest risk in infants <6 mo old

## Pneumonia

- see P93

## Periorbital (Preseptal) and Orbital Cellulitis

- see [Ophthalmology](#), OP10
- preseptal cellulitis ~3 times more common than orbital cellulitis
- causative pathogens include: *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *M. catarrhalis*, *H. influenzae* (less common now due to vaccination)
- key to management is distinguishing between preseptal and orbital cellulitis (which is an OCULAR and MEDICAL EMERGENCY)



### Cardinal Signs of Orbital Involvement

- Ophthalmoplegia/diplopia
- Decreased visual acuity
- Pain with extraocular eye movement

## Sexually Transmitted Infection

- see [Family Medicine](#), FM46 and [Gynecology](#), GY26



## Sinusitis

- see [Family Medicine](#), FM47
- complication of ≤10% of URTIs in children
- clinical diagnosis
- diagnostic imaging is NOT required to confirm diagnosis in children
  - routine CT not recommended, but consider if suspect complications of sinusitis, persistent/recurrent disease, need for surgery
- antibiotic therapy for all children (although nearly half resolve spontaneously within 4 wk)
- complications: preseptal/orbital (cellulitis, orbital abscess, osteomyelitis, etc.), intracranial (meningitis, abscess, etc.), Pott's Puffy tumour



## Urinary Tract Infection (UTI)

### Definition

- infection of the urinary bladder (cystitis) and/or kidneys (pyelonephritis)

### Epidemiology

- overall prevalence in infants and young children presenting with fever is 7%
- <4-6 wk old: more common in boys
- >1 yr old: females have two to four fold higher prevalence

### Etiology

- majority (>95%) have a monomicrobial cause with *E. coli* identified as the causative agent most of the time (~70%)
- Gram-negative bacilli: *E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*
- Gram-positive cocci: *S. saprophyticus*, *Enterococcus*

### Risk Factors

- non-modifiable: female gender, Caucasian, previous UTIs, family history
- modifiable: urinary tract abnormalities (vesicoureteral reflux, neurogenic bladder, obstructive uropathy, posterior urethral valve), dysfunctional voiding, repeated bladder catheterization, uncircumcised males, labial adhesions, sexually active, constipation, toilet training



Bagged urine specimen not useful for ruling in UTI (high false positive rate >85%), but useful for ruling out UTI (high sensitivity).



### Features suggestive of pyelonephritis

- High-grade fever
- Flank or high abdominal pain
- CVA tenderness on palpation

## History

- infants and young child: often just fever or non-specific symptoms (poor feeding, irritability, FTT, jaundice if <28 d old, vomiting)
- older child: fever, urinary symptoms (dysuria, urgency, frequency, incontinence, hematuria), abdominal and/or flank pain

## Physical

- infants and young child: toxic vs non-toxic, febrile, FTT, jaundice; look for external genitalia abnormalities (phimosis, labial adhesions) and lower back signs of occult myelodysplasia (e.g. hair tufts), which may be associated with neurogenic bladder
- older child: febrile, suprapubic and/or CVA tenderness, abdominal mass (enlarged bladder or kidney); may present with short stature, FTT or hypertension secondary to renal scarring from previously unrecognized or recurrent UTIs

## Investigations

- sterile urine specimen
  - clean catch, catheterization or suprapubic aspiration
  - urinalysis (leukocyte esterase, nitrites, erythrocytes), microscopy (bacteria and leukocytes), culture and sensitivity
- diagnosis established if urinalysis suggests infection AND if  $\geq 50,000$  colony-forming units per mL of a uropathogen cultured

## Management

- admit if: <2 mo old, urosepsis, persistent vomiting, inability to tolerate oral medication, moderate-severe dehydration, immunocompromised, complex urologic pathology, inadequate follow-up, failure to respond to outpatient therapy
- supportive care: maintenance of hydration and adequate pain control
- antibiotics
  - base on local antimicrobial susceptibility patterns
  - commence broad empiric therapy until results of urine culture and sensitivity known, and then tailor as appropriate
  - neonates: IV ampicillin and gentamicin
  - infants and older children: oral cephalexin if outpatient; IV ampicillin and gentamicin if inpatient
  - duration 7-14 d
- imaging
  - renal and bladder U/S for all febrile infants with UTIs looking for anatomical abnormalities, hydronephrosis, abscess
  - voiding cystourethrogram (VCUG) not recommended after 1st febrile UTI unless U/S reveals hydronephrosis, obstructive uropathies or other signs suggestive of high-grade vesicoureteral reflux (VUR)
- follow-up: outpatients to return in 24-48 h if no clinical response and seek prompt medical evaluation for future febrile illnesses
- prophylaxis: generally not recommended unless higher grades of VUR

## Complications

- long term morbidity: focal renal scarring develops in 8% of patients; long term significance unknown



### Sensitivity and Specificity of Urine Dip in Children

	Sensitivity	Specificity
Microscopy	73%	81%
Leukocytes		
Nitrites	53%	98%
Leukocyte esterase	83%	78%
Microscopy	81%	83%
Bacteriuria		
Leukocyte esterase, or nitrites, or microscopy positive	99.8%	70%

*Pediatrics* 2011;128:595-610



### Prophylaxis After First Febrile Urinary Tract Infection in Children? A Multicenter, Randomized Controlled, Noninferiority Trial

*Pediatrics* 2008;122:1064-1071

**Study:** Randomized, controlled, open-label, 2 armed, noninferiority trial.

**Patients:** 338 patients aged 2 mo to <7 yr who had a first episode of febrile UTI.

**Intervention:** No prophylaxis vs. prophylaxis

**Outcome:** Recurrence rate of febrile UTI and rate of renal scarring.

**Results:** No significant difference in recurrence rate or in the rate of renal scarring between the prophylaxis and no prophylaxis group.



### Dubowitz/Ballard Scores

GA can be determined after birth using Dubowitz/Ballard scores:

- Assessment at delivery of physical maturity (e.g. plantar creases, lanugo, ear maturation) and neuromuscular-maturity (e.g. posture, arm recoil) translates into a score from -10 to +50
- Higher score means greater maturity (increased GA)
- -10 = 20 wk; +50 = 44 wk
- Ideal = 35-40 which corresponds to GA 38-40 wk
- Only accurate  $\pm 2$  wk

# Neonatology

## Gestational Age (GA) and Size

### Definitions

- classification by gestational age (GA)
  - preterm: <37 wk
  - term: 37-42 wk
  - post-term: >42 wk
- classification by birth weight
  - small for gestational age (SGA): 2 SD < mean weight for GA or <10<sup>th</sup> percentile
  - appropriate for gestational age (AGA): within 2 SD of mean weight for GA
  - large for gestational age (LGA): 2 SD > mean weight for GA or >90<sup>th</sup> percentile

**Table 26. Abnormalities of Gestational Age and Size**

Features	Causes	Problems
<b>Pre-term Infants</b> <37 wk	Spontaneous: cause unknown Maternal disease: hypertension, diabetes, cardiac and renal disorders Fetal conditions: multiple pregnancy, congenital abnormalities Pregnancy issues: placental insufficiency, placenta praevia, uterine malformations, previous preterm birth, infection Behavioural and psychological contributors: smoking, EtOH, drug use, psychosocial stressors Sociodemographic factors: age, socioeconomic conditions	Respiratory distress syndrome, apnea of prematurity, chronic lung disease, bronchopulmonary dysplasia Feeding difficulties, necrotizing enterocolitis (NEC) Hypocalcemia, hypoglycemia, hypothermia Anemia, jaundice Retinopathy of prematurity Intracranial/intraventricular hemorrhage Patent ductus arteriosus (PDA)
<b>Post-term Infants</b> >42 wk Leathery skin Meconium staining	Most cases unknown Increased in first pregnancies Previous post-term birth Genetic factors	Increased risk of stillbirth or neonatal death Increased birthweight Fetal "postmaturity syndrome": impaired growth due to placental dysfunction Meconium aspiration
<b>SGA Infants</b> <10 <sup>th</sup> percentile Asymmetric (head-sparing): late onset, growth arrest	Extrinsic causes: placental insufficiency, poor nutrition, hypertension, multiple pregnancies, drugs, EtOH, smoking	Perinatal hypoxia Hypoglycemia, hypocalcemia, hypothermia, hyperviscosity (polycythemia), jaundice, hypomotility
Symmetric: early onset, lower growth	Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic	Patent ductus arteriosus (PDA)
<b>LGA Infants</b> >90 <sup>th</sup> percentile	Maternal diabetes Racial or familial factors Increasing parity Previous LGA infant, high BMI, large pregnancy weight gain Certain syndromes	Birth trauma, perinatal depression (meconium aspiration, respiratory distress syndrome (infants of diabetic mothers), transient tachypnea of newborn, jaundice, polycythemia, hypoglycemia, hypocalcemia)

## Routine Neonatal Care

- erythromycin ointment: applied to both eyes for prophylaxis of ophthalmia neonatorum
- vitamin K IM: prophylaxis against hemorrhagic disease of newborn
- screening tests
  - in Ontario, newborn screening tests for
    - hearing loss
    - endocrine disorders (congenital adrenal hyperplasia, congenital hypothyroidism)
    - cystic fibrosis
    - hemoglobinopathies (HbSS, HbSc, etc.)
    - inborn errors of metabolism including galactosemia, biotinidase deficiency, fatty acid oxidation defects
- if mother Rh negative: send cord blood for blood group and direct antiglobulin test
- if mother hepatitis B surface antigen positive: HBIG and start hepatitis B vaccine series

## Neonatal Resuscitation

- assess Apgar at 1 and 5 min
- if <7 at 5 min then reassess q5min, until >7
- do not wait to assign Apgar score before initiating resuscitation

**Table 27. Apgar Score**

Sign	0	1	2
<b>Heart Rate</b>	Absent	<100/min	>100/min
<b>Respiratory Effort</b>	Absent	Slow, irregular	Good, crying
<b>Irritability</b>	No response	Grimace	Cough/cry
<b>Tone</b>	Limp	Some flexion of extremities	Active motion
<b>Colour</b>	Blue, pale	Body pink, extremities blue (acrocyanosis)	Completely pink



### Apgar Score

Appearance (colour)  
Pulse (heart rate)  
Grimace (irritability)  
Activity (tone)  
Respiration (respiratory effort)  
Or: "How Ready Is This Child?"

### Initial Resuscitation

- anticipation: know maternal history, history of pregnancy, labour, and delivery
- steps to take for all infants (before ABCs)
  - warm (radiant heater, warm towels) and dry the newborn (remove wet towels)
  - position and clear airway (“sniffing” position)
  - stimulate infant: rub lower back gently or flick soles of feet EXCEPT if meconium present (in which case tracheal suction first)
  - assess breathing and heart rate
- Airway
  - if meconium is present and
    - ♦ baby is vigorous (strong respiratory effort, good muscle tone, HR >100): no further resuscitative interventions required
    - ♦ baby is not vigorous: intubate and suction trachea while monitoring vital signs. If prolonged or unsuccessful intubation, attempt bag mask ventilation
  - if no meconium and suction required, suction mouth first and then nose
- Breathing
  - if HR <100 or apnoeic, apply positive pressure ventilation (PPV)
  - PPV at rate of 40-60/min with enough pressure to see visible chest expansion and note increase in HR
  - if PPV not effective (no increase in HR, no chest rise), incorporate MRSOPA corrective actions
- Circulation
  - if HR <60 after 30 s of effective ventilation, start chest compressions (“60 or less, compress”)
  - should provide 100% oxygen as soon as chest compressions are required
  - chest compressions at lower 1/3 of the sternum and 1/3 of the AP depth at a rate of 120 events per min (3 compressions:1 ventilation = 90 compressions/min:30 breaths/min)



#### MR SOPA

Mask readjustment  
Reposition airway  
Suction mouth and nose  
Open mouth  
Pressure increase  
Alternative airway

**Table 28. Interventions Used in Neonatal Resuscitation**

Intervention	Schedule	Indications	Comments
<b>Epinephrine</b> (adrenalin)	0.1-0.3 mL/kg/dose of 1:10,000 (0.01-0.03 mg/kg) IV 0.05-0.1 mg/kg (0.5-1 mL/kg 1:10,000) endotracheally can be considered while awaiting IV access (IV preferred) Can be repeated q3-5 min prn	HR <60 and not rising	Side effects: tachycardia, hypertension, cardiac arrhythmias
<b>Naloxone</b> (Narcan®)	0.1 mg/kg IV/IM	Not recommended as part of initial resuscitation. HR and oxygenation should be restored by supporting ventilation	Do not use for chronic opiate exposure – may cause withdrawal symptoms including hypertension, irritability, seizures Action of opioid outlasts action of naloxone therefore close monitoring required after administration
<b>Fluid Bolus</b> (NS, whole blood, Ringer's lactate)	10 mL/kg May need to be repeated Not to give too rapidly as large volume rapid infusions can be associated with IVH	Evidence of hypovolemia	

## Approach to the Depressed Newborn

- a depressed newborn lacks one or more of the following characteristics of a normal newborn
  - pulse >100 bpm
  - cries when stimulated
  - actively moves all extremities
  - has a good strong cry
- approximately 10% of newborn babies require assistance with breathing after delivery

**Table 29. Etiology of Respiratory Depression in the Newborn**

Etiology	Examples
<b>Respiratory Problems</b>	Respiratory distress syndrome/Hyaline membrane disease Pulmonary hypoplasia CNS depression Meconium aspiration Pneumonia Pneumothorax Pleural effusions Congenital malformations

**Table 29. Etiology of Respiratory Depression in the Newborn** (continued)

Etiology	Examples
Anemia (severe)	Erythroblastosis fetalis Secondary hydrops fetalis
Maternal Causes	Drugs/anesthesia (opiates, mag sulphate) Diabetes mellitus Maternal myasthenia gravis
Congenital Malformations/Birth Injury	Nuchal cord, perinatal depression Bilateral phrenic nerve injury Potter's sequence
Shock	Antepartum hemorrhage
Congenital Heart Disease	Transposition of the great arteries with intact ventricular septum
Other	Hypothermia Hypoglycemia Infection

**Diagnosis**

- vital signs
- detailed maternal history
  - include prenatal care, illnesses, use of drugs, labour, previous high risk pregnancies, infections during pregnancy, current infections, duration of ruptured membranes, blood type and Rh status, amniotic fluid status, gestational age, meconium, Apgar scores
- clinical findings (observe for signs of respiratory distress: cyanosis, tachypnea, retractions, grunting, temperature instability)
- laboratory results (CBC, ABG, blood type, glucose)
- transillumination
- CXR

**Management**

- ABCs
- intubation and suction if meconium present
- apply tactile stimulation if no meconium
- provide PPV if apneic or HR <100 bpm
- monitor oxygen saturation and heart rate (if HR <60 bpm, start chest compressions)
- provide ventilatory support and treat the underlying cause

## Common Conditions of Neonates

### Apnea

**Definition**

- “periodic breathing”: normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with pauses lasting 5-10 s
- “apnea”: absence of respiratory gas flow for >15 s (or less if associated with bradycardia or desaturation) – 3 types:
  - central: no chest wall movement, no signs of obstruction
  - obstructive: chest wall movement continues against obstructed upper airway, no airflow
  - mixed: combination of central and obstructive apnea

**Differential Diagnosis**

- in term infants, apnea requires full work-up as it can be associated with sepsis
- other causes:
  - CNS
    - ♦ apnea of prematurity (<34 wk): combination of CNS immaturity and obstructive apnea; resolves by 36 wk GA; diagnosis of exclusion
    - ♦ seizures
    - ♦ intracranial hemorrhage (ICH)
    - ♦ hypoxic injury
  - infectious: sepsis, meningitis, necrotizing enterocolitis (NEC)
  - GI: gastroesophageal reflux disease (GERD), aspiration with feeding
  - metabolic: hypoglycemia, hyponatremia, hypocalcemia, IEM
  - cardiovascular: anemia, hypovolemia, PDA, heart failure
  - drugs: morphine

**Management**

- O<sub>2</sub>, ventilatory support, maintain normal blood gases
- tactile stimulation
- correct underlying cause
- medications: methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)

## Bleeding Disorders in Neonates

**Clinical Presentation**

- oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), subgaleal haemorrhage and prolonged bleeding following circumcision

**Approach to Bleeding Disorders in Neonates**

- 4 major categories

**1. increased platelet destruction:**

- maternal ITP, SLE
- neonatal alloimmune thrombocytopenia (NAIT)
- infection
- DIC
- drugs
- extensive localized thrombosis

**2. decreased platelet production/function:**

- bone marrow replacement
- pancytopenia
- Fanconi anemia
- Trisomy 13 and 18

**3. metabolic:**

- congenital thyrotoxicosis
- inborn error of metabolism

**4. coagulation factor deficiencies (see [Hematology](#), H29):**

- hemophilia A
- hemophilia B
- hemorrhagic disease of the newborn



### NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)

**Epidemiology**

- 1 per 4000-5000 live births

**Pathophysiology**

- platelet equivalent of Rh disease of the newborn
- occurs when mother is negative for human platelet antigen (HPA) and fetus is positive
- development of maternal IgG antibodies against HPA antigens on fetal platelets

**Clinical Presentation**

- petechiae, purpura, thrombocytopenia in otherwise healthy neonate
- severe NAIT can lead to intracranial bleeding

**Diagnosis**

- maternal and paternal platelet typing and identification of platelet alloantibodies

**Treatment**

- IVIG to mother prenatally starts in second trimester ± steroids ± fetal platelet transfusions
- treat neonate with IVIG
- if transfusion required should be with washed maternal platelets or donor HPA negative platelets

### AUTOIMMUNE THROMBOCYTOPENIA

**Pathophysiology**

- caused by antiplatelet antibodies from maternal ITP or SLE
- passive transfer of antibodies across placenta

**Clinical Presentation**

- similar presentation to NAIT, but thrombocytopenia usually less severe

**Treatment**

- steroids to mother for 10-14 d prior to delivery or IVIG to mother before delivery
- IVIG infant after delivery (usually if platelets <60,000)
- transfusion of infant with maternal/donor platelets only in severe cases, as antibodies will destroy transfused platelets



**HEMORRHAGIC DISEASE OF THE NEWBORN**

- caused by vitamin K deficiency
- factors II, VII, IX, X are vitamin K-dependent, therefore both PT and PTT are abnormal

**Etiology and Clinical Presentation**

- neonates at risk of vitamin K deficiency if:
  - vitamin K poorly transferred across the placenta
  - maternal use of anticonvulsants
  - insufficient bacterial colonization of colon at birth to synthesize vitamin K
  - dietary intake of vitamin K inadequate in breastfed infants

**Prevention**

- vitamin K IM administration at birth to all newborns

**Bronchopulmonary Dysplasia (BPD)****Definition**

- also known as chronic lung disease (CLD)
- clinically defined as O<sub>2</sub> requirement for >28 d plus persistent need for oxygen and/or ventilatory support at 36 wk corrected GA
- damage to developing lungs with prolonged intubation/ventilation

**Investigations**

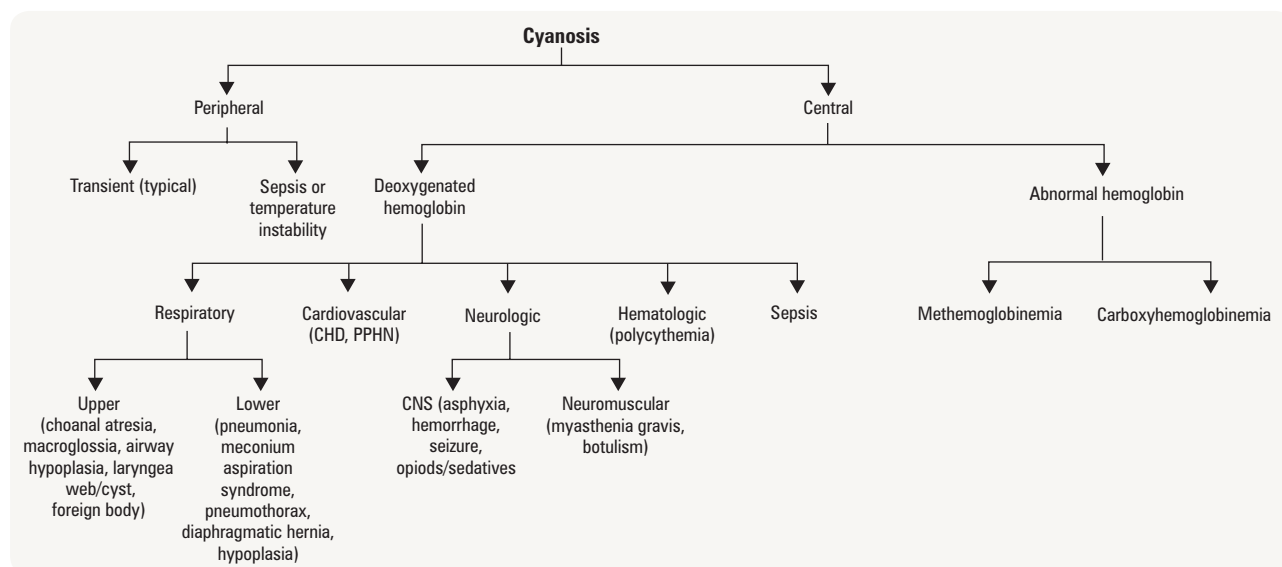
- CXR findings may demonstrate decreased lung volumes, areas of atelectasis and hyperinflation

**Treatment**

- no good treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, but use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcomes

**Prognosis**

- chronic respiratory failure may lead to pulmonary hypertension, poor growth, and right-sided heart failure
- patients with BPD may continue to have significant impairment and deterioration in lung function late into adolescence
- some lung abnormalities may persist into adulthood including airway obstruction, airway hyper-reactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcomes

**Cyanosis****Figure 12. Approach to neonatal cyanosis**

## Management

- ABGs
  - elevated  $\text{CO}_2$  suggests respiratory cause
  - hyperoxia test (to distinguish between cardiac and respiratory causes of cyanosis): get baseline  $\text{PaO}_2$  in room air, then  $\text{PaO}_2$  on 100%  $\text{O}_2$  for 10-15 min
    - ♦  $\text{PaO}_2 < 150$  mmHg: suggests cyanotic congenital heart disease or possible persistent newborn pulmonary hypertension (PPHN) (see *Pediatric Cardiology*, P16)
    - ♦  $\text{pO}_2 > 150$  mmHg: suggests cyanosis likely due to respiratory or non-cardiac cause
- CXR: look for respiratory abnormalities (respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)



**Carboxyhemoglobinemia** (secondary to carbon monoxide poisoning) results in impaired binding of oxygen to hemoglobin but does not discolour the blood. Therefore it may not register on pulse-oximetry and cyanosis may not be evident clinically.

**Methemoglobinemia** pulse oximetry typically reads higher than the true level of oxyhemoglobin. Methemoglobin alters the absorption of red light at the two wavelengths that pulse oximetry uses to predict oxygen saturation.

## Diaphragmatic Hernia

### Definition

- developmental defect of the diaphragm with herniation of abdominal organs into thorax
- associated with pulmonary hypoplasia and PPHN

### Clinical Presentation

- respiratory distress, cyanosis
- scaphoid abdomen and barrel-shaped chest
- affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
- heart sounds shifted to contralateral side
- asymmetric chest movements, trachea deviated away from affected side
- may present outside of neonatal period
- often associated with other anomalies (cardiovascular, CNS, chromosomal abnormalities)
- CXR: bowel loops in thorax (usually left side), displaced mediastinum

### Treatment

- immediate intubation required at birth: DO NOT bag mask ventilate because air will enter stomach and further compress lungs
- place large bore orogastric tube to decompress bowel
- initial stabilization and management of pulmonary hypoplasia and PPHN, hemodynamic support and surgery when stable

## Hypoglycemia

### Definition

- glucose  $< 2.6$  mmol/L (40 mg/dL)

### Etiology

- decreased carbohydrate stores (premature, IUGR)
- infant of a diabetic mother (IDM): maternal hyperglycemia  $\rightarrow$  fetal hyperglycemia and hyperinsulinism  $\rightarrow$  hypoglycemia in the newborn infant because of high insulin levels
- sepsis
- hyperinsulinism due to islet cell hyperplasia (e.g. Beckwith-Wiedemann syndrome)
- panhypopituitarism
- inborn errors of metabolism: fatty acid oxidation defects, galactosemia

### Clinical Findings

- signs often non-specific and subtle: lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

### Management

- identify and monitor infants at risk (pre-feed blood glucose checks)
- begin oral feeds as soon as possible after birth and ensure regular feeds
- if significant and/or symptomatic hypoglycemia, provide glucose IV and titrate according to blood sugar levels
- if persistent hypoglycemia or no predisposing cause for hypoglycemia, send "critical bloodwork" during an episode of hypoglycemia:
 

▪ insulin	▪ lactate
▪ cortisol	▪ ammonia
▪ growth hormone (GH)	▪ free fatty acids (FFAs)
▪ $\beta$ -hydroxybutyrate	▪ ABG
- hyperinsulinism managed with glucagon and/or diazoxide, consultation with pediatric endocrinologist

## Intraventricular Hemorrhage (IVH)

### Definition

- hemorrhage originating in the periventricular subependymal germinal matrix (GM)

### Epidemiology

- incidence and severity inversely proportional to gestational age
- 50% of IVH occurs within 8 h of birth; 90% occurs by day 3

### Risk Factors

- prematurity (<32 wk), BW <1500 g, need for vigorous resuscitation at birth, pneumothorax, ventilated preterm infants, hemodynamic instability, RDS, coagulopathy

### Clinical Presentation

- many infants with IVH are asymptomatic
- subtle signs: apnea, bradycardia, changes in tone or activity, altered level of consciousness
- catastrophic presentation: bulging fontanelle, sudden drop in hematocrit, acidosis, seizures, hypotension

### Classification

- Papile classification
- parenchymal hemorrhage may also occur in the absence of intraventricular hemorrhage
- routine head ultrasound screening of all preterm infants <32 wk or <1500 g gestation throughout NICU stay

### Management of Acute Hemorrhage

- supportive care to maintain blood volume and acid-base status
- avoid fluctuations in blood pressure and cerebral blood flow
- follow-up with serial imaging

### Prognosis

- outcome depends on grade of IVH
- short-term sequelae for severe IVH: mortality, extension of bleed, posthemorrhagic hydrocephalus (PHH), posthemorrhagic infarction, cyst formation
- possible long-term major neurological sequelae: cerebral palsy, cognitive deficits, motor deficits, visual and hearing impairment
- grades I and II hemorrhages have a relatively favourable prognosis
- greatest morbidity and mortality is seen with Grade IV hemorrhage and PHH requiring ventriculoperitoneal shunt placement



#### Papile Classification

Grade I: GM hemorrhage  
Grade II: IVH without ventricular dilatation  
Grade III: IVH with ventricular dilatation  
Grade IV: IVH with parenchymal extension

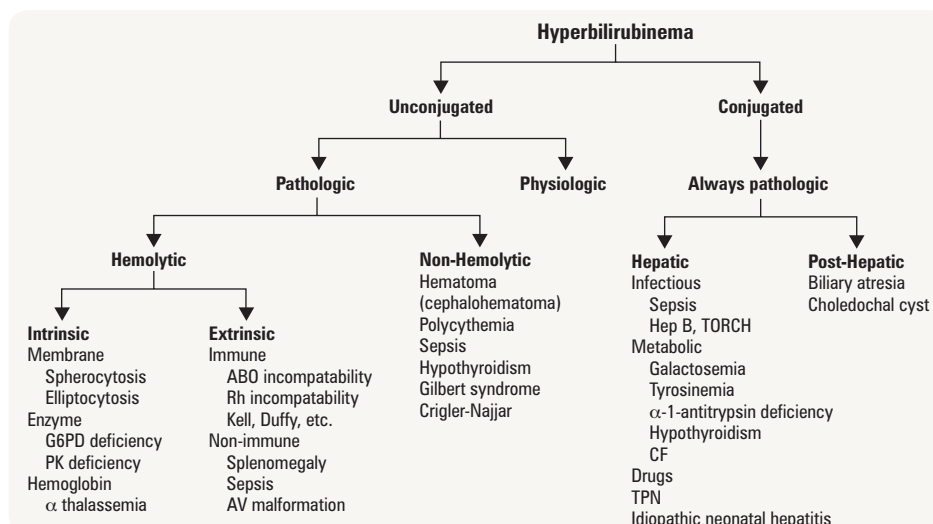
## Jaundice

### Clinical Presentation

- jaundice is visible at serum bilirubin levels of 85-120  $\mu\text{mol/L}$
- look at sclera, tip of nose in natural light
- jaundice more severe/prolonged (due to increased retention of bilirubin in the circulation) with:
  - prematurity, acidosis, hypoalbuminemia, dehydration



Jaundice is very common – 60% of term newborns develop visible jaundice.



Jaundice in the first 24 h and conjugated hyperbilirubinemia are always pathological.

Figure 13. Approach to neonatal hyperbilirubinemia

## PHYSIOLOGIC JAUNDICE

### Epidemiology

- term infants: onset 2-3 d of life, resolution by 7 d of life
- premature infants: higher peak and longer duration

### Pathophysiology

- increased hematocrit and decreased RBC lifespan
- immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
- increased enterohepatic circulation

**Table 30. Risk Factors for Jaundice**

Maternal Factors	Perinatal Factors	Neonatal Factors
Ethnic group (e.g. Asian, native American) Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility) Breastfeeding	Birth trauma (cephalohematoma, ecchymoses) Prematurity	Difficulty establishing breastfeeding Infection Genetic factors Polycythemia Drugs

**Table 31. Causes of Neonatal Jaundice by Age**

<24 h	24-72 h	72-96 h	Prolonged (>1 wk)
<b>ALWAYS PATHOLOGIC</b> Hemolytic Rh or ABO incompatibility Sepsis, e.g. GBS Congenital infection (TORCH) Severe bruising/hemorrhage	Physiologic, polycythemia Dehydration (breastfeeding jaundice) Hemolysis G6PD deficiency Pyruvate kinase deficiency Spherocytosis Bruising, hemorrhage, hematoma Sepsis/congenital infection	Physiologic ± breastfeeding Sepsis	Breast milk jaundice Prolonged physiologic jaundice in preterm Hypothyroidism Neonatal hepatitis Conjugation dysfunction e.g. Gilbert syndrome, Crigler-Najjar syndrome Inborn errors of metabolism e.g. galactosemia Biliary tract obstruction e.g. biliary atresia

### Breastfeeding Jaundice

- common; due to a lack of milk production → dehydration → exaggerated physiologic jaundice

### Breast Milk Jaundice

- 1 per 200 breastfed infants
- glucuronyl transferase inhibitor found in breast milk
- onset 7 d of life, peak at 2-3 wk of life, usually resolved by 6 wk

## PATHOLOGIC JAUNDICE

- must be investigated if:
  - jaundice at <24 h of age
  - serum unconjugated bilirubin rises rapidly or is excessive for patient's age and weight
  - conjugated hyperbilirubinemia
  - persistent jaundice lasting beyond 1-2 wk of age
- investigations
  - unconjugated hyperbilirubinemia:
    - ♦ hemolytic work-up: CBC, reticulocyte count, blood group (mother and infant), peripheral blood smear, Coombs test, bilirubin (conjugated, unconjugated)
    - ♦ if baby is unwell or has fever: septic work-up (CBC and differential, blood and urine cultures ± LP, CXR)
    - ♦ other: G6PD screen (in males), TSH
  - conjugated hyperbilirubinemia: consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic work-up, galactosemia screen (erythrocyte galactose-1-phosphate uridylyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat chloride



### "Bronzed" Baby in Infants with Conjugated Hyperbilirubinemia

Phototherapy results in the production and accumulation of a toxic metabolite which also imparts a bronze hue on the baby's skin.

## TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA

- to prevent kernicterus (see P75)
- breastfeeding does not need to be discontinued, ensure adequate feeds and hydration
- lactation consultant support, mother to pump after feeds
- treat underlying causes (e.g. sepsis)
- phototherapy
  - insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
  - serum bilirubin should be monitored during and immediately after therapy (risk of rebound because photoisomerization reversible when phototherapy discontinued)

- contraindicated in conjugated hyperbilirubinemia: results in “bronzed” baby
- side effects: skin rash, diarrhea, eye damage
- use published guidelines for initiation of phototherapy
- exchange transfusion
  - indications: high bilirubin levels as per published graphs based on age, weeks gestation
  - most commonly performed for hemolytic disease and G6PD deficiency

## KERNICTERUS

### Etiology

- unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin is deposited in the brain resulting in permanent damage (typically basal ganglia or brainstem)
- incidence increases as serum bilirubin levels increase above 340  $\mu\text{mol/L}$  (19.8 mg/dL)
- can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, acidosis, hypothermia, hypoglycemia and prematurity

### Clinical Presentation

- up to 15% of infants have no obvious neurologic symptoms
- early stage: lethargy, hypotonia, poor feeding, emesis
- mid stage: hypertonia, high pitched cry, opisthotonic posturing (back arching), bulging fontanelle, seizures, pulmonary hemorrhage
- late stage (first year and beyond)
  - hypotonia, delayed motor skills, extrapyramidal abnormalities (choreoathetoid cerebral palsy), gaze palsy, mitral regurgitation, sensorineural hearing loss

### Prevention

- exchange transfusion

### Complications

- sensorineural deafness, choreoathetoid cerebral palsy (CP), gaze palsy, mental retardation

## BILIARY ATRESIA

### Definition

- atresia of the extrahepatic bile ducts which leads to cholestasis and increased conjugated bilirubin after the first week of life

### Epidemiology

- incidence: 1:10,000-15,000 live births

### Clinical Presentation

- dark urine, pale stool, jaundice (persisting for >2 wk), abdominal distension, hepatomegaly

### Diagnosis

- conjugated hyperbilirubinemia, abdominal ultrasound
- HIDA scan
- liver biopsy

### Treatment

- surgical drainage procedure
- hepatoportoenterostomy (Kasai procedure; most successful if <8 wk of age)
- usually requires liver transplantation
- vitamins A, D, E, and K; diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

## Necrotizing Enterocolitis (NEC)



### Definition

- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon

### Epidemiology

- affects 1-5% of preterm newborns admitted to NICU

### Pathophysiology

- postulated mechanism of bowel ischemia: mucosal damage and enteral feeding → bacterial growth → bowel necrosis/gangrene/perforation

**Risk Factors**

- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis

**Clinical Presentation**

- distended abdomen
- increased amount of gastric aspirate/vomitus with bile staining
- frank or occult blood in stool
- feeding intolerance
- diminished bowel sounds
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

**Investigations**

- AXR: pneumonitis intestinalis (intramural air is a hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, lactate, blood culture, electrolytes
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnea

**Treatment**

- NPO (7-10 d), vigorous IV fluid resuscitation, decompression with NG tube, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 d)
- serial AXRs detect early perforation
- peritoneal drain/surgery if perforation
- surgical resection of necrotic bowel and surgery for complications (e.g. perforation, strictures)

**Role of Human Milk in Extremely Low Birth Weight Infants' Risk of Necrotizing Enterocolitis or Death**

*J Perinatol* 2009;29:57-62

**Purpose:** To determine if human milk (HM) intake is related to decreased risk of NEC or death.

**Study:** An association between proportion of HM to total intake (enteral and parenteral), enteral intake alone and total volume during the first 14 d after birth to NEC and death was evaluated.

**Patients:** 1272 infants with a birth weight between 401 to 1000 g.

**Main Outcome:** NEC or death occurring between 14 d after birth to 120 d or hospital discharge.

**Results:** For each 10% increase in the proportion of HM to total intake, there was a decrease in likelihood of NEC or death (HR 0.83, 95% CI 0.72 – 0.96). Infants who developed NEC or died were more likely to receive parenteral nutrition only compared to infants who did not develop NEC or death (19 vs. 7.8%).

**Summary:** A reduction in the risk of NEC or death among extremely low birth weight infants was associated with HM feeding. A possible dose-dependent beneficial effect of HM is suggested in extremely low birth weight infants.

## Persistent Pulmonary Hypertension of the Newborn (PPHN)

**Epidemiology**

- incidence 1.9 per 1000 live births

**Clinical Presentation**

- usually presents within 12 h of birth with severe hypoxemia/cyanosis; may have only mild respiratory distress

**Pathophysiology**

- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- R → L shunt through PDA, foramen ovale → decreased pulmonary blood flow and hypoxemia → further pulmonary vasoconstriction

**Risk Factors**

- secondary PPHN: asphyxia, meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), sepsis, pneumonia, structural abnormalities (e.g. diaphragmatic hernia, pulmonary hypoplasia)
- primary PPHN occurs in absence of risk factors

**Investigations**

- measure pre- and post-ductal oxygen levels
- ECHO reveals increased pulmonary arterial pressure and a R → L shunt across PDA and PFO; also used to rule out other cardiac defects

**Treatment**

- maintain good oxygenation (SaO<sub>2</sub> >95%) in at-risk infants
- O<sub>2</sub> given early and tapered slowly, minimize stress and metabolic demands, maintain normal blood gases, circulatory support
- mechanical ventilation, high frequency oscillation (HFO)
- nitric oxide
- extracorporeal membrane oxygenation (ECMO) used in some centres when other therapy fails

## Respiratory Distress in the Newborn

**Clinical Presentation**

- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, subcostal/intercostal indrawing, nasal flaring
- dusky skin, central cyanosis
- decreased air entry, crackles on auscultation



## Differential Diagnosis of Respiratory Distress

- pulmonary
  - respiratory distress syndrome (RDS)
  - transient tachypnea of the newborn (TTN)
  - meconium aspiration syndrome (MAS)
  - pleural effusions, pneumothorax
  - congenital lung malformations
- infectious
  - sepsis, pneumonia
- cardiac
  - congenital heart disease (cyanotic, acyanotic)
  - persistent pulmonary hypertension of the newborn (PPHN)
- hematologic
  - blood loss, polycythemia
- anatomic
  - tracheoesophageal fistula
  - congenital diaphragmatic hernia
  - upper airway obstruction (see [Otolaryngology](#), OT44)
    - ♦ choanal atresia
    - ♦ Pierre-Robin sequence (retrognathia ± micrognathia, cleft palate, glossoptosis)
    - ♦ laryngeal (malacia)
    - ♦ tracheal (malacia, vascular ring)
    - ♦ mucous plug
    - ♦ cleft palate
- metabolic
  - hypoglycemia
  - inborn errors of metabolism (amino acidemia, organic acidemia, urea cycle disturbance, galactosemia, 1° lactic acidosis)
- neurologic
  - CNS damage (trauma, hemorrhage)
  - drug withdrawal syndromes



## Investigations

- CXR, ABG
- CBC, blood cultures, blood glucose
- ECHO, ECG if indicated

**Table 32. Distinguishing Features of RDS, TTN, MAS**

	RDS ("Hyaline Membrane Disease")	TTN ("Wet Lung Syndrome")	MAS
<b>Etiology</b>	Surfactant deficiency → poor lung compliance due to high alveolar surface tension → atelectasis → ↓ surface area for gas exchange → hypoxia + acidosis → respiratory distress	Delayed resorption of fetal lung fluid → accumulation of fluid in peribronchial lymphatics and vascular spaces → tachypnoea	Meconium is sterile but causes airway obstruction, chemical inflammation, and surfactant inactivation
<b>Gestational age</b>	Preterm	More commonly term and late preterm	Term and post-term
<b>Risk Factors</b>	Maternal diabetes Preterm delivery Male sex Low birth weight Acidosis, sepsis Hypothermia Second born twin	Maternal diabetes Maternal asthma Male sex Macrosomia (>4500 g) Elective caesarean section or short labour Late preterm delivery	Meconium-stained amniotic fluid Post-term delivery
<b>Clinical Presentation</b>	Onset within first few hours of life, worsens over next 24-72 h Respiratory distress (tachypnoea, tachycardia, grunting, intercostal indrawing, nasal flaring, cyanosis, lung crackles) Hypoxia Cyanosis	Tachypnoea within the first few hours of life ± retractions, grunting, nasal flaring Often NO hypoxia or cyanosis	Respiratory distress within hours of birth Small airway obstruction, chemical pneumonitis → tachypnea, barrel chest with audible crackles Hypoxia
<b>CXR Findings</b>	Homogenous infiltrates Air bronchograms Decreased lung volumes May resemble pneumonia (GBS) If severe, "white-out" with no differentiation of cardiac border	Perihilar infiltrates "wet silhouette"; fluid in fissures	Hyperinflation Patchy atelectasis Patchy and coarse infiltrates 10-20% have pneumothorax



**Table 32. Distinguishing Features of RDS, TTN, MAS (continued)**

	<b>RDS</b> <b>("Hyaline Membrane Disease")</b>	<b>TTN</b> <b>("Wet Lung Syndrome")</b>	<b>MAS</b>
<b>Prevention</b>	Prenatal corticosteroids (e.g. Celestone® 12 mg q24h x 2 doses) if risk of preterm delivery <34 wk Monitor lecithin:sphingomyelin (L/S) ratio with amniocentesis, L/S >2:1 indicates lung maturity	Where possible, avoidance of elective caesarean delivery, particularly before 38 wk gestation	If infant is depressed at birth, intubate and suction below vocal cords Avoidance of factor associated with in utero passage of meconium, e.g. post term delivery
<b>Treatment</b>	Resuscitation Oxygen Ventilation Surfactant (decreases alveolar surface tension, improves lung compliance and maintains functional residual capacity)	Supportive Oxygen if hypoxic ventilator support (e.g. CPAP) IV fluids and lavage feeds	Resuscitation Oxygen Ventilatory support Surfactant Inhaled nitric oxide, extracorporeal membrane oxygenation at some centres for PPHN
<b>Complications</b>	In severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia (BPD)	Hypoxaemia Hypercapnea Acidosis PPHN	Hypoxaemia Hypercapnoea Acidosis PPHN Pneumothorax Pneumomediastinum Chemical pneumonitis Secondary surfactant inhibition Respiratory failure
<b>Prognosis</b>	Dependent on gestation at birth and severity of underlying lung disease; long term risks of CLD	Recovery usually expected in 2-5 d	Dependent on severity, mortality up to 20%

**PNEUMONIA**

- see *Pediatric Respiriology*, P93
- consider in infants with prolonged or premature rupture of membranes (PROM), maternal fever, or if mother is GBS positive
- suspect if infant exhibits respiratory distress, temperature instability, or WBC is low, elevated or left-shifted
- symptoms may be non-specific
- CXR: hazy lung and/or distinct infiltrates (may be difficult to differentiate from RDS)

**Retinopathy of Prematurity (ROP)**

- see [Ophthalmology](#), OP41

**Common Neonatal Skin Conditions****Table 33. Common Neonatal Skin Conditions**

<b>Neonatal Skin Conditions</b>	<b>Description</b>
<b>Vasomotor Response</b> (Cutis Marmorata, Acrocyanosis)	Transient mottling when exposed to cold; usually normal, particularly if premature
<b>Vernix Caseosa</b>	Soft, creamy, white layer covering baby at birth
<b>Slate-Grey Nevus of Childhood</b> (‘Mongolian spots’)	Bluish grey macules over lower back and buttocks (may look like bruises); common in dark skinned infants
<b>Capillary Hemangioma</b>	Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yr, 90% by 9 yr
<b>Erythema Toxicum</b>	Yellow-white papules surrounded by erythema; common rash, resolves by 2 wk
<b>Milia</b>	Lesions 1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolving
<b>Pustular Melanosis</b>	Brown macular base with pustules, seen more commonly in African American infants; may be present at birth
<b>Angiomatous Lesions (Salmon Patch)</b>	Transitory macular capillary hemangiomas of the eyelids and neck (“Angel Kiss” and “Stork Bite”); usually disappears with age
<b>Neonatal Acne</b>	Inflammatory papules and pustules mainly on face; self-resolving

## Sepsis in the Neonate

**Table 34. Sepsis Considerations in the Neonate**

Early Onset (72 h)	Late Onset (>72 h – 28 d)
Vertical transmission, 95% present within 24 h after birth Risk factors: Maternal infection: UTI, GBS positive, previous child with GBS sepsis or meningitis Maternal fever/leukocytosis/chorioamnionitis Prolonged rupture of membranes (>18 h) Preterm labour Pathogens: GBS, <i>E. coli</i> , <i>Listeria</i> most common Pneumonia more common with early onset sepsis	Acquired after birth Most common in preterm infants in NICU (most commonly due to coagulase negative staphylococcus) Other pathogens implicated include GBS, anaerobes, <i>E. coli</i> , <i>Klebsiella</i> , sepsis and meningitis more common than early onset

### Signs of Sepsis

- no reliable absolute indicator of occult bacteremia in infants <3 mo, most specific result has been WBC <5
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distension, diarrhea
- hypotonia, seizures, lethargy
- jaundice, hepatomegaly, petechiae, purpura



### Chronic Perinatal Infections

#### CHEAP TORCHES

Chicken pox /shingles  
Hepatitis B  
Ebstein-Barr virus  
AIDS (HIV)  
Parvovirus B19 (erythema infectiosum)  
Toxoplasmosis  
Other  
Rubella virus  
Cytomegalovirus/Coxsackievirus  
Herpes simplex virus  
Every STI  
Syphilis

See [Obstetrics](#), OB20

## Nephrology

### Approach to Infant/Child with Dehydration

#### Etiology

- decreased intake: poor oral intake during acute illness, breastfeeding difficulties, eating disorders
- increased losses, common sites include:
  - GI: diarrhea, vomiting, bleeding
  - skin/mucous membranes: fever, burns, hemorrhage, stomatitis
  - urinary: osmolar diuresis (e.g. hyperglycemia, DKA), diuretic therapy, diabetes insipidus, post-obstructive/post ATN recovery diuresis
  - respiratory: tachypnea, bronchiolitis, pneumonia

#### Management

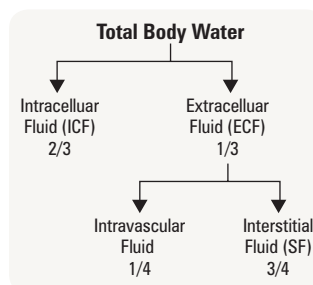
- if suspect dehydration based on history (acute illness, ↓ number of wet diapers, lethargy, changes in mental status, ↑ thirst, etc.), you must:

#### 1) Determine degree of extracellular volume contraction

**Table 35. Assessment of Degree of Extracellular Volume Contraction based on Physical Examination**

	Mild	Moderate	Severe
<2 yr	5%	10%	15%
>2 yr	3%	6%	9%
Pulse (HR)	Normal, full	Rapid	Rapid, weak
Blood Pressure (BP)	Normal	Normal-low	Shock – decreased BP (very late finding in pediatrics and very dangerous)
Urine Output (UO)	Decreased	Markedly decreased	Anuria
Oral Mucosa	Slightly dry	Dry	Parched
Anterior Fontanelle	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin Turgor	Normal	Decreased	Tenting
Capillary Refill	Normal (<3 s)	Normal to increased	Increased (>3 s)

\* Note that percentages refer to percent loss of pre-illness body weight



**Figure 14. Body fluid compartments**



### Electrolyte Concentrations of Na<sup>+</sup> and K<sup>+</sup> (in mEq/L)

	ICF	ECF
Sodium	10	140
Potassium	150	4



### Assessment of Severity of Dehydration

#### C BASE H<sub>2</sub>O

Capillary refill  
BP  
Anterior fontanelle  
Skin turgor  
Eyes sunken  
HR  
Oral mucosa  
Output of urine

2) Determine the likely electrolyte disturbance

- dependent on etiology of dehydration and type of fluid loss (isotonic vs. hypertonic vs. hypotonic) (See Table 36)

Table 36. Electrolyte content of various bodily fluids

Bodily Fluid	Na <sup>+</sup> concentration (mmol/L)	K <sup>+</sup> concentration (mmol/L)	Cl <sup>-</sup> concentration (mmol/L)	HCO <sub>3</sub> <sup>-</sup> concentration (mmol/L)
Saliva	30-80	20	70	30
Gastric juice	60-80	15	100	0
Pancreatic juice	140	5-10	60-90	40-100
Bile	140	5-10	100	40
Small bowel	140	20	100	25-50
Large bowel	75	30	30	0
Sweat	20-70	5-10	40-60	0

- initial investigations should include blood work for ALL patients looking at:
  - electrolyte disturbances (Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>) + glucose
  - acid-base disturbances (blood pH, pCO<sub>2</sub>, HCO<sub>3</sub><sup>-</sup>)
  - impaired renal function (creatinine, BUN)

3) Determine if the child requires oral or intravenous rehydration

- dehydrated child must receive adequate fluid management, including replacement of ongoing losses and providing maintenance fluids
- initial management using oral rehydration therapy (ORT) advantages: ↓ cost, no IV needed, ↓ incidence if iatrogenic hyper/hyponatremia, parental involvement
- indications for intravenous rehydration therapy:
  - severe dehydration, which requires close monitoring and frequent assessment of electrolytes
  - inability to tolerate ORT (e.g. vomiting, alteration in mental status, ileus, monosaccharide malabsorption, etc.)
  - inability to provide ORT
  - failure of ORT in providing adequate rehydration (e.g. persistent diarrhea or vomiting)

4) Return the child to a normal volume and electrolyte status by replacing current deficits and ongoing losses

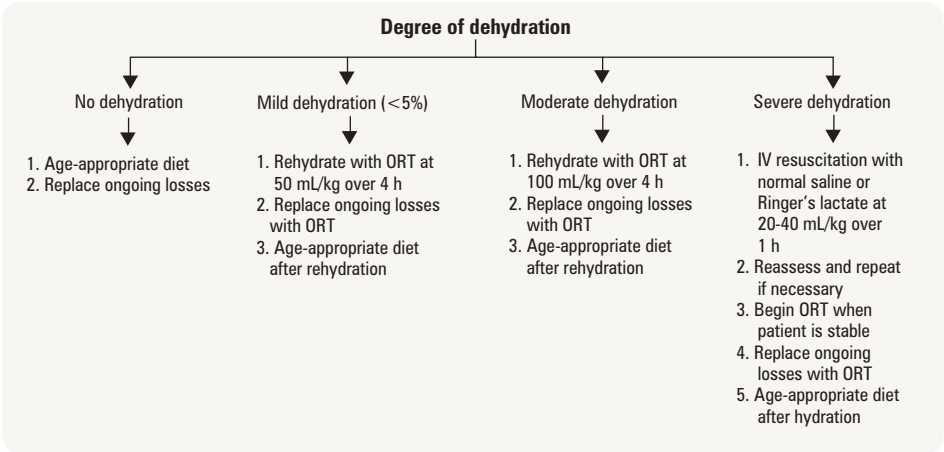


Figure 15. Algorithm for deficit replacement and replacement of ongoing losses in the dehydrated child

## 5) Provide the appropriate fluid and electrolyte maintenance daily requirements (Tables 36 and 37)

**Table 37. Maintenance Fluid Requirements**

Body Weight	100:50:20 Rule (24-h maintenance fluids)	4:2:1 Rule (hourly rate of maintenance fluids)
1-10 kg	100 cc/kg/d	4 cc/kg/h
11-20 kg	50 cc/kg/d	2 cc/kg/h
>20 kg	20 cc/kg/d	1 cc/kg/h

- Types of fluids used:
  - normal saline (NS), Ringer's lactate (RL), half-normal saline (0.45% NaCl), 0.2% NS (for neonates only), D5W, and D10W (for neonates only), add potassium chloride (if hypokalemic)
- Common IV fluid combinations used in pediatrics:
  - first month of life: D5W/0.2 NS + 20 mEq KCl/L (only add KCl if voiding well)
  - children: D5W/NS + 20 mEq KCl/L or D5W/0.45 NS + 20 mEq KCl/L
  - NS: as bolus to restore circulation in dehydrated children (remains almost entirely distributed in intravascular space)
- Correction of Fluid and Electrolyte Deficits
  - if serum  $[Na^+]$  <138-144 mmol/L, use NS or RL
  - if serum  $[Na^+]$  145-154 mmol/L, IV fluid sodium concentration should approximate 0.45 NS
  - if serum  $[Na^+]$  >154 mmol/L, risk of **cerebral edema** with rapid rehydration of hypotonic solutions (i.e. NS) therefore replace fluid slowly with close monitoring.

## 6) Continue to monitor fluid and electrolyte status

- accurate monitoring of daily fluid intake (oral and IV) and ongoing losses (urine output, diarrhea, emesis, drains)
- if child receiving >50% of maintenance fluids through IV, serum electrolyte values should be monitored DAILY and adjusted accordingly
- avoid iatrogenic hyper/hyponatremia, keep the possibility of SIADH in mind



### Special Consideration – Syndrome of Inappropriate ADH (SIADH)

**Clinical Signs:** hyponatremia and excretion of concentrated urine.

**Renal Failure:** certain medications (e.g. morphine), post-op, pain, nausea and vomiting, pulmonary disease (e.g. pneumonia), CNS disease (e.g. meningitis).

**Caution:** acute hyponatremia is associated with rapid administration of hypotonic IV, this can lead to cerebral edema and herniation.

## Common Pediatric Renal Diseases

**Table 38. Common Manifestations of Renal Disease**

Neonate	Common Causes
Flank Mass	Hydronephrosis, polycystic disease (ARPKD or ADPKD), tumour
Hematuria	Renal vein thrombosis, asphyxia, malformation, trauma
Anuria/Oliguria	Bilateral renal agenesis, obstruction, asphyxia
Child and Adolescent	Differential Diagnosis
Cola/Red-Coloured Urine	Acute glomerulonephritis (post-Strep GN, HSP, IgA nephropathy, etc.), hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis)
Gross Hematuria	Urologic disease (nephrolithiasis, trauma, etc.), urinary tract infection (UTI), acute glomerulonephritis
Edema	Nephrotic syndrome, nephritis, acute/chronic renal failure, consider cardiac or liver disease
Hypertension	Glomerulonephritis, renal failure, dysplasia (consider coarctation, drugs, endocrine causes)
Polyuria	DM, central and nephrogenic diabetes insipidus, renal Fanconi's syndrome (genetic/metabolic/acquired causes), hypercalcemia, polyuric renal failure (renal dysplasia)
Proteinuria	Orthostatic, nephrotic syndrome (minimal change disease, etc.), glomerulonephritis
Oliguria	Dehydration, acute tubular necrosis (ATN), interstitial nephritis, acute or chronic kidney disease (i.e. renal failure)
Urgency	UTI, vulvovaginitis

## Hemolytic Uremic Syndrome (HUS)

### Definition

- simultaneous occurrence of the triad of 1) non-immune microangiopathic hemolytic anemia, 2) thrombocytopenia and 3) acute renal injury

### Epidemiology

- annual incidence of 1-2 per 100,000 in Canada
- most common cause of acute renal failure in children

### Etiology

- diarrhea positive HUS: 90% of pediatric HUS from *E. coli* O157:H7 shiga toxin or verotoxin
- diarrhea negative HUS: other bacteria, viruses, familial, drugs

### Pathophysiology

- toxin binds, invades and destroys colonic epithelial cells, causing bloody diarrhea
- toxin enters the systemic circulation, attaches and injures endothelial cells (especially in kidney) causing a release of endothelial products (e.g. von Willebrand factor, platelet aggregating factor)
- form platelet/fibrin thrombi in multiple organ systems (e.g. kidney, pancreas, brain, etc.) resulting in thrombocytopenia
- RBCs are forced through occluded vessels resulting in fragmented RBCs (schistocytes) that are removed by the reticuloendothelial system (hemolytic anemia)

### History and Physical

- initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea
- within 5-7 d begins to show signs of anemia, thrombocytopenia and renal insufficiency
- history: weakness, lethargy, oliguria
- physical exam: pallor, jaundice (hemolysis), edema, petechiae, hypertension

### Investigations

- CBC (anemia, thrombocytopenia), blood smear (schistocytes), electrolytes, renal function, urinalysis (microscopic hematuria), stool cultures and verotoxin/shigella toxin assay

### Management

- mainly supportive: nutrition, hydration, ventilation (if necessary), blood transfusion for symptomatic anemia
- monitor electrolytes and renal function: dialysis if electrolyte abnormality cannot be corrected, fluid overload, or uremia
- steroids are NOT helpful
- antibiotics are contraindicated because death of bacteria leads to increased toxin release and worse clinical course

### Prognosis

- 5-10% mortality, 10-30% renal damage

## Nephritic Syndrome

### Definition

- acute or chronic syndrome affecting the kidney, characterized by glomerular injury and inflammation, and defined by hematuria (>5 RBCs per high-powered microscope field) and the presence of dysmorphic RBCs and RBC casts on urinalysis
- often accompanied by at least one of proteinuria (<50 mg/kg/d), edema, hypertension, azotemia, and oliguria

### Epidemiology

- highest incidence in children aged 5-15 yr old

### Etiology

- humoral immune response to a variety of etiologic agents → immunoglobulin deposition → complement activation, leukocyte recruitment, release of growth factors/cytokines → glomerular inflammation and injury → porous podocytes → hematuria + RBC casts ± proteinuria
- hypertension secondary to fluid retention and increased renin secretion by ischemic kidneys
- primary (idiopathic) versus secondary (to a systemic disease), low complement levels versus normal complement levels (Table 39)

**Table 39. Major Causes of Nephritic Syndrome**

	Decreased C3	Normal C3
<b>Primary</b>	Post-infectious GN (most common cause of acute GN in pediatrics) Membranoproliferative <ul style="list-style-type: none"> <li>• Type I (50-80%)</li> <li>• Type II (&gt;80%)</li> </ul>	IgA Nephropathy Idiopathic rapidly progressive GN Anti-GBM disease
<b>Secondary</b>	SLE Bacterial endocarditis Abscess or shunt nephritis Cryoglobulinemia	Henoch-Schönlein purpura (very common) Polyarteritis nodosa Granulomatosis with polyangiitis (GPA) Goodpasture's syndrome



#### Nephritic Syndrome

##### PHAROH

Proteinuria (<50 mg/kg/d)  
Hematuria  
Azotemia  
RBC casts  
Oliguria  
Hypertension



**Risk Factors**

- recent streptococcal pharyngitis or skin infection, systemic illnesses (see *Etiology of Nephritic Syndrome*, P82)

**History and Physical**

- often asymptomatic; some overlap in clinical findings for nephritic and nephrotic syndrome
- gross hematuria, mild-moderate edema, oliguria
- signs and symptoms suggestive of underlying systemic causes (e.g. fever, arthralgias, rash, dyspnea, pulmonary hemorrhage)

**Investigations**

- urine
  - dipstick (hematuria, 0 to 2+ proteinuria) and microscopy (>5 RBCs per high-powered microscope field, acanthocytes, RBC casts)
  - first morning urine protein/creatinine ratio (<200 mg/mmol)
- blood work
  - impaired renal function (↑ Cr and BUN) resulting in ↓ pH and electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia)
  - mild anemia on CBC (secondary to hematuria)
  - hypoalbuminemia (secondary to proteinuria)
  - appropriate investigations to determine etiology: C3/C4 levels, serologic testing for recent streptococcal infection (ASOT, anti-hyaluronidase, anti-streptokinase, anti-NAD, anti-DNAse B), ANA, anti-DNA antibodies, ANCA, serum IgA levels, anti-GBM antibodies
- renal biopsy
  - should be considered only in presence of: acute renal failure, no evidence of streptococcal infection, normal C3/C4

**Management**

- treat underlying cause
- symptomatic
  - renal insufficiency: supportive (dialysis if necessary), proper hydration
  - hypertension: salt and fluid restriction (but not at expense of renal function), ACE inhibitors or ARBs for chronic persistent HTN (not acute cases since ACE inhibitors or ARBs may decrease GFR further)
  - edema: salt and fluid restriction, possibly diuretics (avoid if significant intravascular depletion)
- corticosteroids if indicated: IgA nephropathy, lupus nephritis, etc.

**Prognosis**

- dependent on underlying etiology
- complications include hypertension, heart failure, pulmonary edema, chronic kidney injury (requiring renal transplant)

## Nephrotic Syndrome

**Definition**

- clinical syndrome affecting the kidney, characterized by significant proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia

**Epidemiology**

- highest incidence in children of 2 to 6 yr old, M>F

**Etiology**

- primary nephrotic syndrome; nephrotic syndrome (NS) in the absence of systemic disease (most common cause in pediatrics)
  - glomerular inflammation ABSENT on renal biopsy: minimal change disease (>90% of all NS), focal segmental glomerular sclerosis (FSGS)
  - glomerular inflammation PRESENT on renal biopsy: membranoproliferative glomerulonephritis, IgA nephropathy, other minor causes
- secondary nephrotic syndrome: NS associated with systemic disease or due to another process causing glomerular injury (very rare in pediatrics)
  - autoimmune: SLE, diabetes mellitus, rheumatoid arthritis, etc.
  - genetic: sickle cell disease, Alport syndrome, etc.
  - infections: HBV/HCV, post-streptococcal, infective endocarditis, HUS, HIV, etc.
  - malignancies: leukemia, lymphoma, etc.
  - medications: captopril, penicillamine, NSAIDs, anticonvulsants, etc.
  - vasculitides: Henoch-Schönlein, GPA, etc.
- congenital nephrotic syndrome: congenital nephropathy of the Finnish type, Denys-Drash syndrome, etc.

**PALE**

Proteinuria (>50 mg/kg/d)  
HypoAlbuminemia (<20 g/L)  
HyperLipidemia  
Edema



Daily protein excretion can be estimated from a random urine protein/creatinine ratio.

**Risk Factors**

- family history, certain systemic illnesses and medications (as per *Etiology*, P83)

**History and Physical**

- non-specific (e.g. irritability, malaise, fatigue, anorexia, diarrhea)
- edema
  - often first sign; detectable when fluid retention exceeds 3 to 5 percent of body weight
  - starts periorbital and often pretibial → edematous areas are white, soft, and pitting
  - gravity dependent: periorbital edema ↓ and pretibial edema ↑ over the day
  - anasarca may develop (i.e. marked periorbital and peripheral edema, ascites, pleural effusions, scrotal/labial edema)
- decrease in effective circulating volume (e.g. tachycardia, hypertension, oliguria, etc.)
- foamy urine is a possible sign of proteinuria

**Investigations**

- urine
  - urine dipstick (3 to 4+ proteinuria, microscopic hematuria) and microscopy (oval fat bodies, hyaline casts)
  - first morning urine protein/creatinine ratio (>200 mg/mmol)
- blood work
  - diagnostic: hypoalbuminemia (<25 g/L), hyperlipidemia/hypercholesterolemia (total cholesterol >5 mmol/L)
  - secondary: electrolytes (hypocalcemia, hyperkalemia, hyponatremia), renal function (↑ BUN and Cr), coagulation profile (↓ PTT)
  - appropriate investigations to rule out secondary causes of NS: CBC, blood smear, C3/C4, ANA, HBV/HCV titers, ASOT, HIV serology, etc.
- consider renal biopsy if:
  - HTN (↑ risk of FSGS), gross hematuria, irenal function, low serum C3/C4
  - no response to steroids after 4 wk of therapy
  - frequent relapses (>2 relapses in 6 mo)
  - presentation before first year of life (high likelihood of congenital nephrotic syndrome)
  - presentation ≥12 yr (rule out more serious renal pathology than minimal change disease)

**Management**

- minimal change disease: oral prednisone 2 mg/kg/d (or equivalent) for up to 12 wk → varicella status should be known before starting
- consider cytotoxic agents, immunomodulators or high-dose pulse corticosteroid if steroid resistant
- symptomatic
  - edema: salt and fluid restriction, possibly diuretic (avoid if significant intravascular depletion); furosemide + albumin for anasarca
  - hyperlipidemia: generally resolves with remission; limit dietary fat intake; consider statin therapy if persistently nephrotic
  - hypoalbuminemia: IV albumin and lasix not routinely given; consider if refractory edema
  - abnormal BP: control BP; fluid resuscitation if severe intravascular depletion; ACE inhibitors or ARBs for persistent HTN
- diet: NAS (no added salt) diet; monitor caloric intake and supplement with Ca<sup>2+</sup> and Vit D if on corticosteroids
- daily weights and blood pressure to assess therapeutic progress
- secondary infections:
  - treat with appropriate antimicrobials; antibiotic prophylaxis not recommended
  - pneumococcal vaccine at diagnosis and varicella vaccine after remission; varicella Ig + acyclovir if exposed while on corticosteroids
- secondary hypercoagulability: mobilize, avoid hemoconcentration due to hypovolemia, prompt sepsis treatment; heparin if thrombi occur

**Prognosis**

- generally good: 80% of children responsive to corticosteroids
- up to 2/3 experience relapse, often multiple times; sustained remission with normal kidney function usually by adolescence
- complications: ↑ risk of infections (spontaneous peritonitis, cellulitis, sepsis); hypercoagulability due to decreased intravascular volume and antithrombin III depletion (pulmonary embolism, renal vein thrombosis; intravascular depletion-hypotension, shock, renal failure; side effects of drugs)

**Long-term steroid use associated with:**

- Increased appetite
- Impaired growth
- Behavioural changes
- Risk of infection
- Salt and water retention
- Hypertension
- Bone demineralization

## Hypertension in Childhood

### Definition

- hypertension: systolic and/or diastolic blood pressure (BP) that is  $\geq 95$ th percentile for sex, age and height (Table 40) on  $\geq 3$  occasions
- prehypertension: systolic and/or diastolic BP  $\geq 90$ th percentile but  $< 95$ th percentile OR BP  $\geq 120/80$  irrespective of age, gender and height

**Table 40. 95th Percentile Blood Pressures (mmHg)**

Age (Years)	Female		Male	
	50th Percentile for Height	75th Percentile for Height	50th Percentile for Height	75th Percentile for Height
1	104/58	105/59	102/57	104/58
6	111/73	112/73	114/74	115/75
12	123/80	124/81	123/81	125/82
17	129/84	130/85	136/87	138/88

Adapted from Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents working group report from the National High Blood Pressure Education Program

### Epidemiology

- increasing prevalence of both hypertension and prehypertension over the last 25+ yr
- prevalence: 3-5% for hypertension, 7-10% for prehypertension; M>F

### Etiology

- primary HTN
  - diagnosis of exclusion
  - most common in older children ( $\geq 10$  yr), especially if positive family history, overweight and only mild hypertension
  - responsible for  $\sim 90\%$  of cases of HTN in adolescents, rarely in young children
- secondary HTN
  - identifiable cause of HTN
  - responsible for majority of childhood hypertension
  - most likely etiology dependent on age (see Table 41), renal parenchymal disease most common cause (60 to 70% of cases)
- always consider white coat HTN for all ages

**Table 41. Etiology of Secondary Hypertension by Age Group**

System	Neonates	1 month to 6 years	7-12 years	>13 years
<b>Endocrine/Metabolic</b>	Congenital adrenal hyperplasia	Wilms' tumour ( $\uparrow$ renin) Neuroblastoma ( $\uparrow$ catecholamines)	Endocrinopathies*	Endocrinopathies*
<b>Renal</b>	Congenital renal disease	Renal parenchymal disease	Renal parenchymal disease	Renal parenchymal disease
<b>Vascular</b>	Coarctation of the aorta Renal artery thrombosis	Coarctation of the aorta Renal artery stenosis (RAS)	Renovascular abnormalities	
<b>Drugs</b>		Corticosteroids Cyclosporine and tacrolimus	Corticosteroids OCP Cyclosporine and tacrolimus	Corticosteroids OCP Cyclosporine and tacrolimus Recreational drugs (amphetamines, cocaine, etc.)
<b>Other</b>			iatrogenic	iatrogenic

\*Note: endocrinopathies may include hyperthyroid, hyperparathyroid, Cushing's syndrome, primary hyperaldosteronism/Conn's syndrome, pheochromocytoma

### Risk Factors

- primary HTN: male gender, positive family history, metabolic syndrome, OSA, African-American, prematurity/low-birth weight
- secondary HTN: history of renal disease, abdominal trauma, family history of autoimmune diseases, umbilical artery catheterization

### History

- often asymptomatic, but can include FTT, fatigue, epistaxis
- symptoms of hypertensive emergency
  - neurologic: headache, seizures, focal complaints, change in mental status, visual disturbances
  - cardiovascular: symptoms of MI or heart failure (chest pain, palpitations, cough, shortness of breath)
- symptoms of secondary HTN: guided by etiology above; ask about medications and recreational drugs (current and past)

**Physical**

- BP measurement (make sure correct cuff size is used), plot on growth chart, BMI
- look for signs of hypertensive emergency (e.g. full neurologic exam, ophthalmoscopy, precordial exam, peripheral pulses, perfusion status)
- look for signs of secondary HTN

**Investigations**

- laboratory:
  - urine dipstick for hematuria and/or proteinuria (renal disease), urine catecholamines (pheochromocytoma, neuroblastoma)
  - blood work: renal function tests (electrolytes, Cr, BUN), consider renin and aldosterone levels (RAS, Conn's syndrome, Wilms' tumour)
  - other specific hormones if indicated on history and physical
- imaging: echocardiography (coarctation, heart function), abdominal U/S (RAS, abdominal mass), renal radionuclide imaging (renal scarring)
- other: ocular exam

**Management**

- treat underlying cause
- non-pharmacologic: modify concurrent cardiovascular risk factors (rate reduction, exercise, salt restriction, smoking cessation, etc.)
- pharmacologic: gradual lowering of BP using thiazide diuretics; no antihypertensives have been formally studied in children; if hypertensive emergencies: hydralazine, labetalol, sodium nitroprusside
- management of end organ damage (e.g. retinopathy, LVH)
- consider referral to specialist

**Prognosis**

- end-organ damage (similar to adults) including: left ventricular hypertrophy, CHF, cerebrovascular insults, renal disease, retinopathy

**Signs of Secondary HTN**

- Edema (renal parenchymal disease)
- Abdominal or renal bruit (RAS)
- Differential 4 limb BP/diminished femoral pulses (coarctation)
- Abdominal mass (Wilms', neuroblastoma)
- Goiter/skin changes (hyperthyroidism)
- Ambiguous genitalia (CAH)

**Pediatric Blood Pressure Calculation**

sBP = age x 2 + 90

dBP = 2/3 x sBP

## Neurology

### Seizure Disorders

- see [Neurology](#), N14

**Differential Diagnosis of Seizures in Children**

- benign febrile seizure
- CNS
  - infection, tumour, hypoxic ischemic encephalopathy
  - trauma, hemorrhage
- metabolic causes (e.g. hypoglycemia, hypocalcemia, hyponatremia)
- idiopathic epilepsy and epileptic syndromes
- others:
  - neurocutaneous syndromes
  - arteriovenous malformation
  - drug ingestions/withdrawal
- seizure mimics

**Investigations**

- lab tests: CBC, electrolytes, calcium, magnesium, glucose
- toxicology screen if indicated
- EEG,
- CT/MRI, if indicated, e.g. focal neurological deficit or has not returned to baseline after several hours after seizure
- LP, if first-time non-febrile seizure but not indicated for determining recurrence risk of benign febrile seizures or to determine seizure type or epileptic syndrome



Heart problems, such as long QT syndrome and hypertrophic cardiomyopathy, are often misdiagnosed as epilepsy. Include cardiac causes of syncope in your differential diagnosis, particularly when the episodes occur during physical activity.

**Seizure Mimics**

- Breath holding
- Night terror
- Benign paroxysmal vertigo
- Narcolepsy
- Pseudoseizure
- Syncope
- Tic
- Hypoglycemia
- TIA

**CHILDHOOD EPILEPTIC SYNDROMES****Infantile Spasms**

- brief, repeated symmetric contractions of neck, trunk, extremities (flexion and extension) lasting 10-30 s
- occur in clusters; often associated with developmental delay; onset 4-8 mo
- 20% unknown etiology (usually good response to treatment); 80% due to metabolic or developmental abnormalities, encephalopathies, or are associated with neurocutaneous syndromes (usually poor response to treatment)

- can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hyperarrhythmia) or Lennox Gastaut (see below)
- typical EEG: hypsarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
- management: ACTH, vigabatrin, benzodiazepines

### Lennox-Gastaut

- characterized by triad of 1) multiple seizure types, 2) diffuse cognitive dysfunction and 3) slow generalized spike and slow wave EEG
- onset commonly 3-5 yr of age
- seen with underlying encephalopathy and brain malformations
- management: valproic acid, benzodiazepines and ketogenic diet; however, response often poor

### Juvenile Myoclonic Epilepsy (Janz Syndrome)

- myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
- adolescent onset (12-16 yr of age); autosomal dominant with variable penetrance
- typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
- management: lifelong treatment (valproic acid); excellent prognosis

### Childhood Absence Epilepsy

- multiple daily absence seizures lasting <30 s without post-ictal state that may resolve spontaneously or become generalized in adolescence
- peak age of onset 6-7, F>M, strong genetic predisposition
- typical EEG: 3/s spike and wave
- management: valproic acid or ethosuximide

### Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes

- focal motor seizures involving tongue, mouth, face, upper extremity usually occurring in sleep-wake transition states; remains conscious, but aphasic post-ictally
- onset peaks at 5-10 yr of age, 16% of all non-febrile seizures; remits spontaneously in adolescence without sequelae
- typical EEG: repetitive spikes in centrotemporal area with normal background
- management: frequent seizures controlled by carbamazepine, no medication if infrequent seizures

### General Approach to Treatment

- medication
  - initiate: treatment with drug appropriate to seizure type; often initiate anticonvulsants if >2 unprovoked afebrile seizures within 6-12 mo
  - optimize: start with one drug and increase dosage until seizures controlled
  - if no effect, switch over to another before adding a second anticonvulsant
  - continue anticonvulsant treatment until patient free of seizures for >2 yr, then wean medications over 4-6 mo
- ketogenic diet (high fat diet): used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- education for patient and parents including education and precautions in daily life (e.g. buddy system, showers instead of baths)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

### Generalized and Partial Seizures

- see [Neurology](#), N14



#### Ketogenic Diet and other Dietary Treatments for Epilepsy

*Cochrane DB of Syst Rev* 2012;3:CD001903

**Study:** Systematic review of all studies of ketogenic and related diets. Included the review of 4 RCTs, 6 prospective studies and 5 retrospective studies.

**Population:** Adults and children with diagnosed epilepsy of any type.

**Intervention:** Ketogenic diet, control (placebo diet, any treatment with known antiepileptic properties)

**Main outcome measure:** Seizure control at 3, 6, 12 mo.

**Results:** Studies showed a response rate of at least 38-50% seizure reduction at 3 mo. This response was maintained for up to a year. A range of side effects were reported. The most frequent were gastrointestinal effects (30%).

**Conclusion:** The ketogenic diet is a valid option for people with medically-intractable epilepsy.



## Febrile Seizures

### Epidemiology

- most common cause of seizure in children (3-5% of children)
- M>F; age 6 mo-6 yr

### Clinical Presentation

- short (~1 min, always <5 min) generalized tonic-clonic seizure with short post-ictal state
- often with associated illness or fever and family history
- no evidence of CNS infection/inflammation before or after seizure; no history of non-febrile seizures

**Table 42. Comparison of Simple and Complex Febrile Seizures**

Simple/Benign (70-80%)	Complex/Atypical (20-30%)
Duration <15 min (95% <5 min)	Duration >15 min
Generalized tonic-clonic	Focal onset or focal features during seizure
No recurrence in 24-h period	Recurrent seizures (>1 in 24-h period)
No neurological impairment or developmental delay before or after seizure	Previous neurological impairment or neurological deficit after seizure

} any one of

**Workup**

- history: determine focus of fever, description of seizure, medications, trauma history, development, family history
- exam: LOC, signs of meningitis, neurological exam, head circumference, focus of infection
- septic work-up including LP if suspecting meningitis (strongly consider if child <12 mo; consider if child is 12-18 mo; only if meningeal sign present if child >18 mo)
- if simple febrile seizure, investigations only for determining focus of fever
- EEG not warranted unless complex febrile seizure or abnormal neurologic findings

**Management**

- counsel and reassure patient and parents:
  - febrile seizures do not cause brain damage
  - very small risk of developing epilepsy: 9% in child with multiple risk factors (i.e. development or neurological abnormalities prior to seizure, family history of complex febrile seizure, multiple simple febrile seizure); 2% in child with febrile simple seizures compared to 1% in general population
  - 33% chance of recurrence (mostly within 1 yr of first seizure and in children <1 yr old)
- antipyretics (e.g. acetaminophen) and fluids for comfort (though neither prevent seizure)
- prophylaxis not recommended
- if high risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home
- treat underlying cause of fever

## Recurrent Headache

- see [Neurology](#), N38

**Differential Diagnosis**

- primary headache: tension, migraine, cluster
- secondary headache: see [Neurology](#), N39

**General Assessment**

- if unremarkable history and neurological and general physical exam is negative, most likely diagnosis is migraine or tension-type headache
- CT or MRI if history or physical reveals red flags
- inquire about level of disability, academic performance, after-school activities

**MIGRAINE**

- 4-5% of school aged children; F>M after puberty
- heterogeneous autosomal dominant inheritance with incomplete penetrance (majority of patients have a positive family history)

**Types**

- common (no aura): most common in children, often with intense nausea and vomiting
- classic (with aura)
- complicated: basilar, ophthalmoplegic, confusional, hemiplegic

**Clinical Features**

- infancy: spells of irritability, sleepiness, pallor, and vomiting
- young child: periodic headaches with nausea and vomiting that is relieved by rest
- older child: usually unilateral throbbing headaches with photophobia or phonophobia

**Prognosis and Treatment**

- >50% undergo spontaneous prolonged remission after 10 yr of age
- non-pharmacological treatment and prophylaxis: rest in quiet, dark room, avoid triggers (poor sleep, stress, chocolate, caffeine), biofeedback techniques, exercise, magnesium supplementation
- pharmacological treatment: early analgesia (e.g. ibuprofen), sumatriptan or other triptans if >12 yr of age
- pharmacological prophylaxis:  $\beta$ -blockers (e.g. propranolol), antihistamines, antidepressants (e.g. amitriptyline/nortriptyline), calcium-channel blockers, anticonvulsants (e.g. divalproex sodium)

**Headache – Red Flags**

- New headache
- Worst headache of their lives
- Acute onset
- Focal neurological deficits
- Constitutional symptoms
- Worse in morning
- Worse with bending over, coughing, straining
- Change in level of consciousness
- Sudden mood changes
- Disturbed sleep
- Fatigue
- Withdrawal from social activities
- Chronic systemic signs (e.g. weight loss, fever, anorexia, focal neurological signs)



## TENSION HEADACHES

### Clinical Features

- usually bilateral pressing tightness (aching, non-throbbing) anywhere on the cranium
- building in intensity; lasting 30 min-days
- no nausea/vomiting, not aggravated by physical activity

### Management

- reassurance, supportive counseling (e.g. explain how stress may cause a headache)
- rule out refractory errors in eyesight
- mild analgesia (NSAIDs, acetaminophen)

## ORGANIC HEADACHES

- organic etiology often suggested with occipital headache especially in pre-school aged child and red flags (e.g. ataxia)
- with increased ICP
  - etiology: brain tumours, hydrocephalus, meningitis, encephalitis, cerebral abscess, pseudotumour cerebri, subdural hematoma
  - characteristics: diffuse early morning headaches, early morning vomiting, headache worsened by increased ICP (cough, sneeze, Valsalva); as ICP increases, headache is constant and child is lethargic and irritable
- without increased ICP
  - etiology: cerebral arteriovenous malformation (AVM), aneurysm, collagen vascular diseases, subarachnoid hemorrhage, stroke

## Hypotonia

- decreased resistance to passive movements – “floppy baby”

### Differential Diagnosis

- central
  - chromosomal (Down, Prader-Willi, Fragile X syndromes)
  - metabolic (hypoglycemia, kernicterus)
  - perinatal problems (asphyxia, ICH)
  - endocrine (hypothyroidism, hypopituitarism)
  - infections (TORCH)
  - CNS malformations
  - dysmorphic syndromes
- peripheral
  - motor neuron (e.g. spinal muscular atrophy, polio)
  - peripheral nerve (e.g. Charcot-Marie-Tooth syndrome)
  - neuromuscular junction (e.g. myasthenia gravis)
  - muscle fibres (e.g. mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

### History and Physical

- proper assessment of tone requires accurate determination of gestational age
- differentiate between upper motor neuron from lower motor neuron signs; spontaneous posture (spontaneous movement, movement against gravity, frog-leg position); muscle weakness; joint mobility (hyperextensibility); muscle bulk, presence of fasciculations
- postural maneuvers:
  - traction response: pull to sit, look for flexion of arms to counteract traction and head lag
  - axillary suspension: suspend infant by holding at axilla and lifting; hypotonic babies will slip through grasp because of low shoulder girdle tone
  - ventral suspension: infant is prone and supported under the abdomen by one hand; infant should be able to hold up extremities; inverted “U” posturing demonstrates hypotonia, i.e. baby will drape self over examiner’s arms
- dysmorphic features, cognitive ability, reflexes, power

### Investigations

- rule out systemic disorders (e.g. blood glucose, CK and serum/urine investigations for multiple etiologies including mitochondrial causes)
- neuroimaging: MRI/MRS when indicated
- EMG, muscle biopsy/NCS
- chromosome analysis, genetic testing, metabolic testing, neuromuscular testing

### Treatment

- depends on etiology: some treatments available for specific diagnosis
- counsel parents on prognosis and genetic implications
- refer patients for specialized care, refer for rehabilitation, OT, PT, assess feeding ability



Causes of hypotonia that respond to rapid treatment: hypokalemia, hypermagnesemia, acidemia, toxins, drugs, hypoglycemia, seizure, infection, intracranial bleeding, hydrocephalus.

## Cerebral Palsy (CP)

### Definition

- a symptom complex, not a disease
- non-progressive central motor impairment syndrome due to insult to or anomaly of the immature CNS
- incidence: 1.5-2.5 per 1000 live births (industrialized nations)
- life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion

### Etiology

- often obscure, no definite etiology identified in 1/3 of cases
- 10% related to intrapartum asphyxia; 10% due to postnatal insult (infections, asphyxia, prematurity with intraventricular hemorrhage and trauma)
- association with low birth weight babies

### Clinical Presentation

**Table 43. Types of Cerebral Palsy**

Type	% of Total CP	Characteristics	Area of Brain Involved
<b>Spastic</b>	70-80%	Truncal hypotonia in 1 <sup>st</sup> yr Increased tone, increased reflexes, clonus Affects one limb (monoplegia), one side of body (hemiplegia), both legs (diplegia), both arms and legs (quadriplegia)	UMN of pyramidal tract Diplegia associated with periventricular leukomalacia in premature babies Quadriplegia associated with HIE (asphyxia), associated with higher incidence of MR
<b>Athetoid/Dyskinetic</b>	10-15%	Athetosis (involuntary writhing movements) ± chorea (involuntary jerky movements) Can involve face, tongue (results in dysarthria)	Basal ganglia (may be associated with kernicterus)
<b>Ataxic</b>	<5%	Poor coordination, poor balance (wide based gait) Can have intention tremor	Cerebellum
<b>Mixed</b>	10-15%	More than one of the above motor patterns	

### Other Signs

- uncoordinated swallowing → aspiration
- microcephaly (25%)
- seizures
- mental retardation, learning disabilities
- delay in motor milestones
- visual, hearing impairment

### Investigations

- may include metabolics, chromosome studies, serology, neuroimaging, EMG, EEG (if seizures), ophthalmology, audiology

### Treatment

- maximize potential through multidisciplinary services such as primary care physician, OT, PT, SLP, school supports, etc.
- orthopedic management (e.g. dislocations, contractures, rhizotomy)
- management of symptoms: spasticity (baclofen, Botox®), constipation (stool softeners)

## Neurocutaneous Syndromes

- characterized by tendency to form tumours of the CNS, PNS, viscera and skin

### Neurofibromatosis Type I (NF-1)

- autosomal dominant but 50% are the result of new mutations
- also known as von Recklinghausen disease
- incidence 1:3000, mutation in *NF1* gene on 17q11.2 (codes for neurofibromin protein)
- learning disorders, abnormal speech development and seizures are common
- diagnosis of NF-1 requires 2 or more of:
  - ≥6 café-au-lait spots (>5 mm if prepubertal, >1.5 cm if postpubertal)
  - ≥2 neurofibromas of any type or one plexiform neurofibroma
  - ≥2 Lisch nodules (hamartomas of the iris)
  - optic glioma
  - freckling in the axillary or inguinal region
  - a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
  - a first degree relative with confirmed NF-1



In neurocutaneous syndromes, the younger the child at presentation, the more likely they are to develop mental retardation.

**Neurofibromatosis Type II (NF-2)**

- autosomal dominant
- incidence 1:33,000
- characterized by predisposition to form intracranial, spinal tumours
- diagnosed when either bilateral vestibular schwannomas found, or a first-degree relative with NF-2 and either a neurofibroma, meningioma, glioma, or schwannoma
- also associated with posterior subcapsular cataracts
- treatment consists of monitoring for tumour development and surgery

**Sturge-Weber Syndrome**

- port-wine nevus syndrome in V1 distribution with associated angiomatous malformations of the brain causing contralateral hemiparesis and hemiatrophy
- also associated with seizure, glaucoma and mental retardation

**Tuberous Sclerosis**

- autosomal dominant inheritance; 50% new mutations
- adenoma sebaceum (angiokeratomas on face, often in malar distribution), Shagreen patch (isolated raised plaque over lower back, buttocks), "ash leaf" hypopigmentation seen with Wood's lamp (UV light)
- cardiac rhabdomyomas, kidney angiomyolipoma, mental retardation and seizures
- cerebral cortex tubers (areas of cerebral dysplasia); subependymal nodules (SEN) may evolve into giant cell astrocytomas (may cause obstructive hydrocephalus)
- calcifications within the SEN are seen on CT, MRI (especially around the foramen of Monro)
  - these may obstruct the foramen and cause hydrocephalus

**Acute Disseminated Encephalomyelitis (ADEM)****Epidemiology**

- median age of onset 5-8 yr; male predominance
- annual incidence in North America is estimated to be 0.4 per 100,000 children <20 yr of age

**Pathophysiology**

- immune-mediated inflammatory disorder of the CNS; characterized by a widespread demyelination predominantly affecting the white matter of the brain and spinal cord (similar to multiple sclerosis)
- usually preceded by a viral infection or vaccination
- absence of clear precedent event has been reported in 26% of patients

**Clinical Presentation**

- often occurs 2 d to 4 wk after a clinically evident infection or vaccination
- clinical course is rapidly progressive, develops over hours to maximum deficits within days
- headache, nausea, vomiting, pyrexia, malaise
- rapid onset encephalopathy, multifocal deficits, seizures
- pyramidal syndrome, cerebellar ataxia, brainstem involvement

**Investigations**

- LP: CSF showing variable pleocytosis and oligoclonal banding
- MRI: large, multifocal, poorly marginated regions of demyelination affecting bilateral subcortical white matter, and deep grey matter (thalamus, basal ganglia); lesions show complete or partial resolution on follow-up, with absence of new clinically silent lesions

**Treatment**

- high dose corticosteroids and supportive measures

**Prognosis**

- favourable, though some residual deficits often exist

# Respirology

## Approach to Dyspnea

- see Table 1, *Average Vitals at Various Ages*, P3

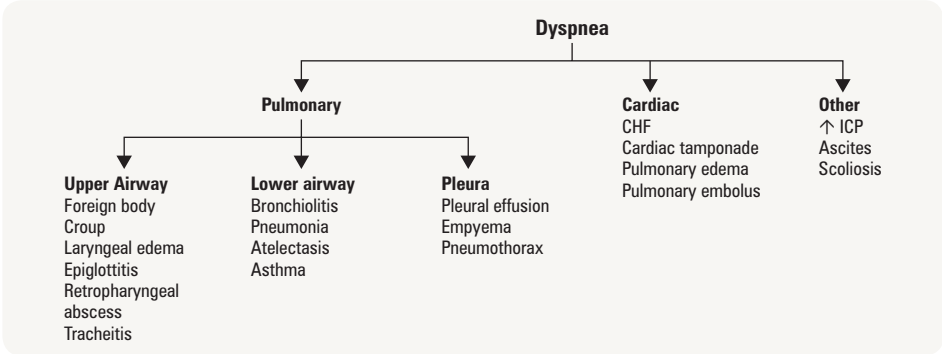


Figure 16. Approach to dyspnea in childhood

## Upper Respiratory Tract Diseases



- see [Otolaryngology](#), OT44
- diseases above the thoracic inlet characterized by inspiratory stridor, hoarseness, and suprasternal retractions
- differential diagnosis of stridor: croup, bacterial tracheitis, epiglottitis, foreign body aspiration, subglottic stenosis (congenital or iatrogenic), laryngomalacia/tracheomalacia (collapse of airway cartilage on inspiration)

Table 44. Common Upper Respiratory Tract Infections in Children

	Croup (Laryngotracheobronchitis)	Bacterial Tracheitis	Epiglottitis
Anatomy	Subglottic laryngitis	Subglottic tracheitis	Supraglottic laryngitis
Epidemiology	Common in children <6 yr, with peak incidence between 7-36 mo Common in fall and early winter	Rare All age groups	Very rare – due to Hib vaccination Usually older (2-6 yr)
Etiology	Parainfluenza (75%) Influenza A and B RSV Adenovirus	<i>S. aureus</i> <i>H. influenzae</i> $\alpha$ -hemolytic strep Pneumococcus <i>Moraxella catarrhalis</i>	<i>H. influenzae</i> $\beta$ -hemolytic strep
Clinical Presentation	Common Prodrome: rhinorrhea, pharyngitis, cough, $\pm$ low-grade fever Symptoms: Hoarse voice Barking cough Stridor Worse at night	Similar symptoms as croup but more rapid deterioration with high fever Toxic appearance Does not respond to croup treatments	Toxic appearance Rapid progression 4 Ds – drooling, dysphagia, dysphonia, distress Stridor Tripod position Sternal recession Anxious Fever ( $>39^{\circ}\text{C}$ )
Investigations	Clinical diagnosis CXR in atypical presentation: “steep sign” from subglottic narrowing	Clinical diagnosis Endoscopy: definitive diagnosis	Clinical diagnosis Avoid examining the throat to prevent further respiratory exacerbation
Treatment	No evidence for humidified $\text{O}_2$ Dexamethasone: PO 1 dose Racemic epinephrine: nebulized, 1-3 doses, q1-2h Intubation if unresponsive to treatment	Usually requires intubation IV antibiotics	Intubation Antibiotics Prevented with Hib vaccine

## Lower Respiratory Tract Diseases

- obstruction of airways below thoracic inlet, produces more expiratory sounds
- classic symptom: wheezing

### Differential Diagnosis of Wheezing

- common
  - asthma: recurrent wheezing episodes, identifiable triggers; typically over 6 yr
  - bronchiolitis: first episode of wheezing; usually under 1 yr
  - recurrent aspiration: often neurological impairment
  - pneumonia: fever, cough, malaise
- uncommon
  - foreign body: acute unilateral wheezing and coughing
  - cystic fibrosis: prolonged wheezing, unresponsive to therapy
  - bronchopulmonary dysplasia: often develops after prolonged ventilation in the newborn
- rare
  - congestive heart failure
  - mediastinal mass
  - bronchiolitis obliterans
  - tracheobronchial anomalies

## Pneumonia

### Etiology

- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

### Clinical Presentation

- incidence is greatest in first year of life with viral cause being most common in children <5 yr
- cough, wheeze, stridor
- CXR: diffuse, streaky infiltrates bilaterally
- bacterial causes may present with cough, fever, chills, dyspnea, more dramatic CXR changes (e.g. lobar consolidation, pleural effusion)

### Management

- see Table 45
- supportive therapy: hydration, antipyretics, humidified O<sub>2</sub>

**Table 45. Common Causes and Treatment of Pneumonia at Different Ages**

Age	Bacterial	Viral	Atypical Bacteria	Treatment
Neonates	GBS <i>E. coli</i> <i>Listeria</i>	CMV Herpes virus Enterovirus	<i>Mycoplasma hominis</i> <i>Ureaplasma urealyticum</i>	ampicillin + gentamicin / tobramycin (add erythromycin if suspect <i>Chlamydia</i> )
1-3 months	<i>S. aureus</i> <i>H. influenzae</i> <i>S. pneumoniae</i> <i>B. pertussis</i>	CMV, RSV Influenza virus Parainfluenza virus	<i>Chlamydia trachomatis</i> <i>Ureaplasma</i>	cefuroxime OR ampicillin ± erythromycin OR clarithromycin
3 months – 5 years	<i>S. pneumoniae</i> <i>S. aureus</i> <i>H. influenzae</i> GAS	RSV Adenovirus Influenza virus	<i>M. pneumoniae</i> , TB	amoxicillin (if mild) OR ampicillin OR cefuroxime
>5 years	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>S. aureus</i>	Influenza virus Varicella Adenovirus	<i>Mycoplasma pneumoniae</i> (most common) <i>Chlamydia pneumoniae</i> TB <i>Legionella pneumophila</i>	erythromycin OR clarithromycin (1st line) OR ampicillin OR cefuroxime

## Bronchiolitis

### Definition

- LRTI that has wheezing and signs of respiratory distress

### Epidemiology

- the most common LRTI in infants, affects 50% of children in first 2 yr of life; peak incidence at 6 mo, winter or early spring
- increased incidence of asthma in later life

### Etiology

- respiratory syncytial virus (RSV) (>50%), parainfluenza, influenza, rhinovirus, adenovirus, *M. pneumoniae* (rare)

### Clinical Presentation

- prodrome of URTI with cough and fever
- feeding difficulties, irritability
- wheezing, respiratory distress, tachypnea, tachycardia, retractions, poor air entry lasting for 5-6 d

### Investigations

- CXR (only in severe disease, poor response to therapy, chronic episode)
  - air trapping, peribronchial thickening, atelectasis, increased linear markings
- nasopharyngeal swab
  - direct detection of viral antigen (immunofluorescence)
- WBC can be normal

### Treatment

- self-limiting disease with symptoms usually lasting 2-3 wk
- mild distress
  - supportive: oral or IV hydration, antipyretics for fever, O<sub>2</sub>
- moderate to severe distress
  - as above ± intubation and ventilation as needed
  - consider rebetol (Ribavirin®) in high risk groups: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodeficient
- monthly RSV-Ig or palivizumab (monoclonal antibody against the F-glycoprotein of RSV) is protective against severe disease in high risk groups; case fatality rate <1%
- antibiotics have no therapeutic value unless there is secondary bacterial pneumonia
- indications for hospitalization:
  - hypoxia: O<sub>2</sub> saturation <92% on initial presentation
  - persistent resting tachypnea >60/min and retractions after several salbutamol masks
  - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
  - young infants <6 mo old (unless extremely mild)
  - significant feeding problems
  - social problem (e.g. inadequate care at home)



#### Bronchodilators for Bronchiolitis

*Cochrane DB Syst Rev 2010;12:CD001266*

**Study:** Meta-analysis of prospective, randomized, double-blinded, placebo-controlled trials.

**Patients:** 1912 infants (28 trials) up to 24 mo old with bronchiolitis.

**Intervention:** Bronchodilators (including albuterol, salbutamol, terbutaline, ipratropium bromide, and adrenergic agents) given oral, subcutaneous, or nebulized vs. placebo.

**Main outcome:** Oxygen saturation.

**Results:** No clinically significant difference for infants treated with bronchodilators vs. placebo for bronchiolitis. Given the costs and side effects it is not recommended to use bronchodilators as management for bronchiolitis in infants.



Children with bronchiolitis do not respond to ipratropium (Atrovent®) or steroids.

## Asthma

### Definition

- see [Respirology](#), R6
- characterized by recurrent episodes of airway hyperreactivity, bronchospasm and inflammation; reversible small airway obstruction
- very common, presents most often in early childhood
- associated with other atopic diseases such as allergic rhinitis or atopic dermatitis



### Clinical Presentation

- episodic bouts of wheezing, dyspnea, tachypnea, cough (usually at night/early morning, with activity or cold exposure)
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze

### Triggers

- URTI (viral or *Mycoplasma*), weather (cold exposure, humidity changes), allergens (pets), irritants (cigarette smoke), exercise, emotional stress, drugs (Aspirin®, β-blockers)

### Classification

- mild asthma
  - occasional attacks of wheezing or coughing (<2/wk)
  - symptoms respond quickly to inhaled bronchodilator
  - never needs systemic corticosteroids
- moderate asthma
  - more frequent episodes with symptoms persisting and chronic cough
  - decreased exercise tolerance
  - sometimes needs systemic corticosteroids
- severe asthma
  - daily and nocturnal symptoms
  - frequent ER visits and hospitalizations
  - usually needs systemic corticosteroid



## Management

- acute
  - O<sub>2</sub> (keep O<sub>2</sub> saturation >92%) and fluids if dehydrated
  - β<sub>2</sub>-agonists: salbutamol (Ventolin®) 0.03 cc/kg (max 1 cc) in 3 cc NS q20min by mask until improvement, then masks hourly if necessary
  - ipratropium bromide (Atrovent®) if severe: 1 cc added to each of first 3 salbutamol masks
  - steroids: prednisone (2 mg/kg in ER, then 1 mg/kg daily x 4 d) or dexamethasone (0.3 mg/kg/d); in severe disease, use IV steroids
  - continue to observe- can discharge patient if asymptomatic for 2-4 h after last dose
- chronic
  - education, emotional support, avoid allergens or irritants, develop an “action plan”
  - exercise program (e.g. swimming)
  - monitor respiratory function with peak flow meter (improves self-awareness of status)
  - PFTs for children >6 yr
  - reliever therapy: short acting β<sub>2</sub>-agonists (e.g. salbutamol)
  - controller therapy (first line therapy for all children): low dose daily inhaled corticosteroids
  - second line therapy for children <12 yr: moderate dose of daily inhaled corticosteroids
  - second line therapy for children >12 yr: antileukotriene OR long acting β<sub>2</sub>-agonist in conjunction with low dose inhaled corticosteroids
    - ♦ leukotriene receptor antagonist monotherapy may be considered an alternative second line therapy
  - severe asthma unresponsive to first and second line treatments injection immunotherapy
  - aerochamber for children using daily inhaled corticosteroids
- indications for hospitalization
  - pre-treatment O<sub>2</sub> saturation <92%
  - past history of life-threatening asthma (ICU admission)
  - unable to stabilize with masks q4h
  - concern over environmental issues or family's ability to cope



### Canadian Paediatric Asthma Consensus Guidelines for assessing adequate control of asthma:

- Daytime symptoms <4 d/wk
- Night time symptoms <1 night/wk
- Normal physical activity
- Mild and infrequent exacerbations
- No work/school absenteeism
- Need for β-agonist <4 doses/wk
- FEV<sub>1</sub> or peak expiratory flow ≥90% of personal best
- Peak expiratory flow diurnal variation <10 to 15%

## Cystic Fibrosis (CF)

- see [Respirology](#), R11

### Etiology

- 1 per 3000 live births, mostly Caucasians
- autosomal recessive, *CFTR* gene found on chromosome 7 (ΔF508 mutation in 70%, but >1600 different mutations identified) resulting in a dysfunctional chloride channel on the apical membrane of cells
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction
- in Ontario, CF is routinely screened in the newborn

### Clinical Presentation

- neonatal
  - meconium ileus
  - prolonged jaundice
  - antenatal bowel perforation
- infancy
  - pancreatic insufficiency with steatorrhea and failure to thrive (despite voracious appetite)
  - anemia, hypoproteinemia, hyponatremia
- childhood
  - heat intolerance
  - wheezing or chronic cough
  - recurrent chest infections (*S. aureus*, *P. aeruginosa*, *H. influenzae*)
  - hemoptysis
  - nasal polyps
  - distal intestinal obstruction syndrome, rectal prolapse
  - clubbing of fingers
- older patients
  - chronic obstructive pulmonary disease
  - infertility (males); decreased fertility (female)

### Investigations

- sweat chloride test x 2 (>60 mEq/L)
  - false positive tests: malnutrition, atopic dermatitis, hypothyroidism, hypoparathyroidism, glycogen storage disease type, adrenal insufficiency, G6PD, Klinefelter syndrome, technical issues, autonomic dysfunction, familial cholestasis syndrome
  - false negative tests: technical problem with test, malnutrition, skin edema, mineralocorticoids



### CF Presenting Signs

#### CF PANCREAS

- Chronic cough and wheezing
- Failure to thrive
- Pancreatic insufficiency (symptoms of malabsorption like steatorrhea)
- Alkalosis and hypotonic dehydration
- Neonatal intestinal obstruction (meconium ileus)/Nasal polyps
- Clubbing of fingers/Chest radiograph with characteristic changes
- Rectal prolapse
- Electrolyte elevation in sweat, salty skin
- Absence or congenital atresia of vas deferens
- Sputum with *Staph* or *Pseudomonas* (mucoid)
- Pancreatic dysfunction – determined by 3 d fecal fat collection
- Genetics – useful where sweat chloride test is equivocal

## Management

- nutritional counselling
  - high calorie diet, pancreatic enzyme replacements, fat soluble vitamin supplements
- management of chest disease
  - physiotherapy, postural drainage
  - exercise
  - bronchodilators
  - aerosolized DNAase and inhaled hypertonic saline
  - antibiotics: depends on sputum C&S (e.g. cephalosporin, cloxacillin, ciprofloxacin, inhaled tobramycin)
  - lung transplantation
- genetic counselling

## Complications

- respiratory failure, pneumothorax (poor prognostic sign), cor pulmonale (late), pancreatic fibrosis with diabetes mellitus, gallstones, cirrhosis with portal hypertension, infertility (male)
- early death (current median survival in Canada is 46.6 yr)

# Rheumatology

## Evaluation of Limb Pain

**Table 46. Differential Diagnosis of Limb Pain**

Cause	<3 yr	3-10 yr	>10 yr
<b>Trauma</b>	x	x	x
<b>Infectious</b>			
Septic arthritis	x	x	x
Osteomyelitis	x	x	x
<b>Inflammatory</b>			
Transient synovitis	x	x	
JIA	x	x	x
Spondyloarthritis		x	x
SLE		x	x
Dermatomyositis		x	x
HSP		x	x
<b>Anatomic/Orthopedic</b>			
Legg-Calve-Perthes disease		x	x
Slipped capital femoral epiphysis			x
Osgood-Schlatter disease			x
<b>Neoplastic</b>			
Leukemia	x	x	x
Neuroblastoma	x	x	x
Bone tumour		x	x
<b>Hematologic</b>			
Hemophilia (hemarthrosis)	x	x	x
Sickle cell anemia	x	x	x
<b>Pain Syndromes</b>			
Growing pains		x	x
Fibromyalgia		x	x
Reflex sympathetic dystrophy			x



### Red Flags for Limb Pain

Fever, pinpoint pain/tenderness, pain out of proportion to degree of inflammation, night pain, weight loss, erythema.

- must rule out infection, malignancy or an acute orthopedic condition

## History

- limp/weight-bearing status
- morning stiffness
- systemic symptoms (fever, rash, weight loss, fatigue)
- past medical illness, intercurrent infection, travel, sick contact history
- family history (arthritis, bleeding disorders, sickle cell anemia, IBD, psoriasis)

**Physical**

- joint exam (swelling, erythema, warmth, tenderness, deformity, ROM)
- adjacent structures (bone, tendon, muscle, skin)
- gait
- leg length
- neurologic exam

**Investigations**

- basic: CBC and differential, blood smear, ESR, CRP, x-ray
- as indicated: blood (ANA, RF, culture, viral/bacterial serology, CK, PTT, sickle cell screen, immunoglobulins, complement), urinalysis, synovial fluid (cell count, Gram stain, culture), TB skin test, imaging, BM aspiration, slit lamp exam

## Growing Pains

**Epidemiology**

- age 2-12 yr, M=F

**Clinical Presentation**

- diagnosis of exclusion
- intermittent, non-articular pain in childhood with *normal physical exam findings*
- pain at night, often limited to the calf, shin or thigh; typically short-lived and bilateral
- relieved by heat, massage, mild analgesics
- child is well, asymptomatic during the day, no functional limitation
- possible family history of growing pains

**Management**

- lab investigations not necessary if typical presentation; reassurance and supportive management

## Transient Synovitis of the Hip

- benign, self limited disorder, usually occurs after upper respiratory tract infection, pharyngitis, otitis media

**Epidemiology**

- age 3-10 yr, M>F

**Clinical Presentation**

- afebrile or low-grade fever, pain typically occurs in hips, knees (referred from hip); painful limp but capable of moving hip through ROM (pain not as pronounced as in joint or bone infections)
- symptoms resolve over 7-10 d

**Investigations**

- WBC within normal limits; ESR and CRP may be mildly elevated
- joint effusions may be seen on imaging
- diagnosis of exclusion (r/o septic arthritis and osteomyelitis)

**Treatment**

- symptomatic and anti-inflammatory medications

## Septic Arthritis

- **MEDICAL EMERGENCY**
- see [Orthopedics](#), ORI0



**Table 47. Microorganisms Involved in Septic Arthritis/Osteomyelitis**

Age	Pathogens	Treatment
Neonate	GBS, <i>S. aureus</i> , GNB	cloxacillin + aminoglycoside or cefotaxime
Infant (1-3 mo)	<i>Strep. sp.</i> , <i>Staph. sp.</i> , <i>H. influenzae</i> Pathogens as per neonate	cloxacillin + cefotaxime
Child	<i>S. aureus</i> , <i>S. pneumoniae</i> , GAS	cefazolin
Adolescent	As above; also <i>N. gonorrhoeae</i>	cefazolin
Sickle cell disease	As above; also <i>Salmonella</i>	cefotaxime

GBS = group B Strep; GNB = Gram-negative bacilli; GAS = group A Strep

Adapted from Tse SML, Laxer RM. Pediatrics in Review 2006;27:170-179

## Juvenile Idiopathic Arthritis (JIA)

- a heterogeneous group of conditions characterized by persistent arthritis in children <16 yr
- arthritis defined:
  1. joint swelling/effusion OR
  2. >2 of the following:
    - ♦ decreased range of motion
    - ♦ tenderness or pain on motion
    - ♦ increased warmth
- diagnosis
  - arthritis in ≥1 joint(s)
  - duration ≥6 wk
  - onset age <16 yr old
  - with exclusion of other causes of arthritis
  - classification defined by features/number of joints affected in the first 6 mo of onset

### Systemic Arthritis (Still's disease)

- onset at any age, M=F
- once or twice daily fever spikes ( $>38.5^{\circ}\text{C}$ )  $\geq 2$  wk; children usually acutely unwell during fever episodes
- extra-articular features: erythematous "salmon-coloured" maculopapular rash, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia, serositis
- arthritis may occur weeks to months later
- high ESR, CRP, WBC, platelet count

### Oligoarticular Arthritis (arthritis of 1-4 joints)

- onset early childhood, F>M
- persistent: affects no more than 4 joints during the disease course
- extended: affects more than 4 joints after the first six months
- typically affects large joints: knees > ankles, elbows, wrists; hip involvement unusual
- ANA positive ~60-80%, rheumatoid factor (RF) negative
- screening eye exams for asymptomatic anterior uveitis (occurs in ~30%)
- complications: knee flexion contracture, quadriceps atrophy, leg-length discrepancy, growth disturbances

### Polyarticular Arthritis (arthritis of 5 or more joints)

- RF negative
  - onset: 2-4 yr and 6-12 yr, F>M
  - symmetrical involvement of large and small joints of hands and feet, TMJ, cervical spine
- RF positive
  - onset: late childhood/early adolescence, F>M
  - similar to the aggressive form of adult rheumatoid arthritis
  - severe, rapidly destructive, symmetrical arthritis of large and small joints
  - may have rheumatoid nodules at pressure points (elbows, knees)
  - unremitting disease, persists into adulthood

### Enthesitis-Related Arthritis

- onset: late childhood/adolescence, M>F
- arthritis and/or enthesitis
- weight bearing joints, especially hip and intertarsal joints
- risk of developing ankylosing spondylitis in adulthood

### Psoriatic Arthritis

- onset: 2-4 yr and 9-11 yr, F>M
- arthritis and psoriasis OR arthritis and at least two of:
  - dactylitis, nail abnormalities, or family history of psoriasis in a 1st degree relative
  - asymmetric or symmetric small or large joint involvement

### Undifferentiated

- arthritis of unknown cause that persists for 6 wk and either does not fulfill criteria for any category or fulfills criteria for more than one category

### Management

- goals of therapy: eliminate inflammation, prevent joint damage, promote normal growth and development as well as normal function, minimize medication toxicity
- exercise to maintain range of motion (ROM) and muscle strength
- multidisciplinary approach: OT/PT, social work, orthopedics, ophthalmology, rheumatology
- 1st line drug therapy: NSAIDs, intra-articular corticosteroids

- 2nd line drug therapy:
  - DMARDs: methotrexate, sulfasalazine, leflunamide
  - corticosteroids: acute management of severe arthritis, systemic symptoms of JIA, topical eye drops for uveitis
  - biologic agents

## Reactive Arthritis

- see [Rheumatology](#), RH23
- arthritis (typically the knee) follows bacterial infection especially with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Chlamydia*, and most commonly *Streptococcus* (post-streptococcal reactive arthritis)
- typically resolves spontaneously
- may progress to chronic illness or Reiter's syndrome (urethritis, conjunctivitis)



## Lyme Arthritis

- see [Infectious Diseases](#), ID26
- caused by spirochete *Borrelia burgdorferi*
- incidence highest among 5-10 yr olds
- do not treat children <8 yr old with doxycycline (may cause permanent tooth discolouration)



## Systemic Lupus Erythematosus (SLE)

- see [Rheumatology](#), RH11
- autoimmune illness affecting multiple organ systems
- incidence 1 per 1000, more commonly age >10, F:M = 10:1
- childhood-onset SLE vs. adult-onset SLE:
  - children have more active disease
  - children are more likely to have renal disease
  - children receive more intensive drug therapy and sustain more damage



## Vasculitides

### HENOCH-SCHÖNLEIN PURPURA (HSP)

- most common vasculitis of childhood, peak incidence 4-10 yr, M:F = 2:1
- vasculitis of small vessels
- often have history of URTI 1-3 wk before onset of symptoms

### Clinical Presentation

- clinical triad: 1) palpable purpura, 2) abdominal pain, 3) arthritis
- skin: palpable, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthralgia involving large joints associated with painful edema
- GI: abdominal pain, GI bleeding, intussusception
- renal: microscopic hematuria, IgA nephropathy, proteinuria, hypertension, renal failure in <5%

### Management

- mainly supportive
- anti-inflammatories for joint pain, corticosteroids for select patients
- monitor for protein on urinalysis every month for 6 mo, checking for renal disease, which may develop late (immunosuppressive therapy if severe)

### Prognosis

- self-limited, resolves within 4 wk
- recurrence in about one third of patients
- long term prognosis dependent on severity of nephritis

## KAWASAKI DISEASE

- acute vasculitis of unknown etiology (likely triggered by infection)
- medium-sized vasculitis with predilection for coronary arteries
- most common cause of acquired heart disease in children in developed countries
- peak age: 3 mo – 5 yr; Asians > Blacks > Caucasians

### Diagnostic Criteria

- fever persisting 5 d or more AND
- 4 of the following features:
  1. bilateral conjunctival injection
  2. red infected fissured lips, strawberry tongue, injected pharynx
  3. changes of the peripheral extremities
    - ♦ acute phase: peripheral edema, peripheral erythema
    - ♦ subacute phase: peeling from tips of fingers and toes
  4. polymorphous rash
  5. cervical lymphadenopathy >1.5 cm in diameter
- exclusion of other diseases (e.g. scarlet fever, measles)
- atypical Kawasaki disease: less than 5 of 6 diagnostic features but coronary artery involvement

### Management

- high (anti-inflammatory) dose of ASA while febrile
- low (anti-platelet) dose of ASA in subacute phase until platelets normalize or longer if coronary artery involvement
- IV immunoglobulin (2 g/kg) within 10 d of onset reduces risk of coronary aneurysm formation
- baseline 2D-ECHO and follow up periodic 2D-ECHO (usually at 6 wk)

### Complications

- coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children, <5% if receive IVIG within 10 d of fever
- 50% of aneurysms regress within 2 yr
- anticoagulation for multiple or large coronary aneurysms
- risk factors for coronary disease: male, age <1 or >9 yr, fever >10 d, Asian or Hispanic ethnicity, thrombocytopenia, hyponatremia



#### Diagnostic Criteria for Kawasaki Disease

Warm CREAM  
 Fever ≥5 d  
 Conjunctivitis  
 Rash  
 Edema/Erythema (hands and feet)  
 Adenopathy  
 Mucosal involvement

## Common Medications

**Table 48. Commonly Used Medications in Pediatrics**

Drug Name	Dosing Schedule	Indications	Comments
acetaminophen (Tylenol®)	10-15 mg/kg/dose PO q4-6h prn	Analgesic, antipyretic	Not to exceed 60 mg/kg/d or 4 g/d Causes hepatotoxicity at high doses
amoxicillin (Amoxil®)	80-90 mg/kg/d PO divided q8h	Otitis media	
dexamethasone	0.6 mg/kg PO x 1 0.3 mg/kg/d PO for 5 d	Croup Acute asthma	
fluticasone (Flovent®)	moderate dose – 250-500 µg/d divided bid high dose – >500 µg/d divided bid	Asthma	
ibuprofen (Advil®)	5-10 mg/kg/dose PO q6-8h	Analgesic, antipyretic	Cautious use in patients with liver impairment, history of GI bleeding or ulcers
iron	6 mg/kg/d elemental iron OD or divided tid	Anemia	SE: dark stool, constipation, dark urine
omeprazole		GERD	SE: headache, diarrhea, nausea, abdominal pain
ondansetron		Post-op nausea and vomiting, gastroenteritis, cyclic vomiting	SE: QTc prolongation, orally disintegrating tablets contain phenylalanine (caution in phenylketonuria patients)
phenobarbital	3-5 mg/kg/d PO OD or bid	Seizures	SE: CNS depression
polyethylene glycol 3350 (PEG)	Disimpaction: 1-1.5 g/kg/d for 3 d Maintenance: Starting dose at 0.4-1 g/kg		



**Table 48. Commonly Used Medications in Pediatrics** (continued)

Drug Name	Dosing Schedule	Indications	Comments
prednisone	1-2 mg/kg/d PO x 5 d	Asthma	Oral prednisone is bitter tasting, consider using prednisilone
prednisilone	3-4 mg/kg/d PO then taper to 1-2 mg/kg/d	ITP	
	PO once platelet count >30 x 10 <sup>9</sup> /L	Nephrotic syndrome	
	60 mg/m <sup>2</sup> /d PO		
salbutamol (Ventolin®)	0.01-0.03 mL/kg/dose in 3 mL normal saline via nebulizer q1/2-4h pm	Acute asthma	Can cause tachycardia, hypokalemia, restlessness
	100-200 µg/dose pm, max 4-8 puffs frequency q4h	Maintenance treatment or asthma	

From Lau, E. (2009) The 2010-2011 Formulary – The Hospital for Sick Children

## References

### Cardiology

Bhandar A, Bhandari V. Pitfalls, problems, and progress in bronchopulmonary dysplasia. *Pediatrics* 2009;123:1562-1573.  
 Ganz, L. Sinus tachycardia. UpToDate, 2012.  
 National Heart, Lung, and Blood Institute (Bethesda, Maryland). Task force on blood pressure control in children: report of the second task force on blood pressure control in children. *Pediatrics* 1987;79:1-25.  
 Smythe J. Does every childhood heart murmur need an echocardiogram? *Can J Ped* 2(4).

### Endocrinology

American Diabetes Association. Type 2 diabetes in children and adolescents. *Pediatrics* 2000;105:671-681.  
 Lenhard MJ, Reeves GD. Continuous subcutaneous insulin infusion: a comprehensive review of insulin pump therapy. *Arch Int Med* 2001;161:2293-3000.  
 Muir A, et al. Precocious puberty. *Ped Rev* 2006;27:373-380.  
 Styne DM, Glaser NS. Nelson's Essentials of Pediatrics, 4th ed. WB Saunders, 2002. Endocrinology; p711-766.

### Gastroenterology

Canadian Pediatric Society, Dieticians of Canada, Health Canada. Nutrition for healthy infants – statement of the joint working group.  
 Friedman JN. Risk of acute hyponatremia in hospitalized children and youth receiving maintenance intravenous fluids. *Canadian Pediatric Society*, 2013.  
 Kirshner BS, Black DD. Nelson's Essentials of Pediatrics, 3rd ed. The gastrointestinal tract. p419-458, 1998.  
 Rowan-Legg A. Oral health care for children: a call for action. *Canadian Pediatric Society*, 2013.  
 Scott, RB. Recurrent abdominal pain during childhood. *Can Fam Phys* 1994;40:539-547.

### General Topics

Albright EK. Pediatric history and physical examination, 4th ed. Current Clinical Strategies Publishing, 2003.  
 Critch JN. Nutrition for healthy term infants, birth to six months: an overview. *Can Ped Soc*, 2013.  
 D'Augustine S, Flosi T. Tarascon pediatric outpatient pocketbook, 1st ed. Tarascon Publishing, 2008.  
 Dipchand A, Friedman J, Bismilla Z, Gupta S, Lam C. The Hospital for Sick Children handbook of pediatrics, 11th ed. Toronto: Elsevier Canada, 2009.  
 Greer FR, et al. Effects of nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;129:183-191.  
 Hospital for Sick Children. Clinical Practice Guidelines: fluid and electrolyte administration in children, 2011.  
 Hospital for Sick Children handbook of pediatric emergency medicine. Sudbury: Jones and Bartlett, 2008.  
 Lau E. 2010-2011 Drug handbook and formulary. Toronto: Hospital for Sick Children Department of Pharmacy, 2009.  
 McGahren ED, Wilson WG. Pediatrics recall, 3rd ed. Baltimore: Lippincott Williams & Wilkins, 2008.  
 Medical Council of Canada. Objectives for the qualifying examination, 3rd ed. 2004.  
 Nelson essentials of pediatrics, 5th ed. Philadelphia: Elsevier Saunders, 2006.  
 Pediatric Emergency Medicine. Apparent life-threatening events. Saunders Elsevier, 2008. p269-272.  
 Publicly founded immunization schedules for Ontario. August 2011.  
 Scruggs K, Johnson MT. Pediatrics 5-minute reviews. Current Clinical Strategies Publishing, 2001-2002.  
 Shields M. Measured obesity: overweight canadian children and adolescents. Nutrition findings from the Canadian Community Health Survey. Statistics Canada, 2005.  
 Zimmerman EP. Male circumcision. *Pediatrics* 2012.

### Genetic Disorders and Developmental Disorders

Amato RSS. Human genetics and dysmorphology. Nelson's Essentials of Pediatrics, 3rd ed. WB Saunders, 2002. p129-146.  
 Blake KD, Prasad C. CHARGE syndrome, orphanet. *J Rare Diseases* 2006;1.  
 Biggar VV. Duchenne muscular dystrophy. *Ped in Rev* 2006;27:83-88.  
 Chudley AE, Conry J, Cook JL, Look C, Rosales T, LeBlanc N (Public Health Agency of Canada's National Advisory Committee on fetal alcohol spectrum disorder). Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. *CMAJ* 2005;172(5 Suppl):S1-21.  
 Nicholson JF. Nelson's Essentials of Pediatrics, 4th ed. WB Saunders, 2002. Inborn errors of metabolism. p153-178.  
 Vissers LE, et al. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nature Genetics* 2004;36:955-957.

### Hematology

Baker RD, Greer FR, Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 yr of age). *Pediatrics* 2010;126:1040-1050.  
 Corrigan J, Boineau F. Hemolytic-uremic syndrome. *Ped in Rev* 2001;22:365-369.  
 Pearce JM, Sills RH. Childhood leukemia. *Ped in Rev* 2005;26:96-102.  
 Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010;115:168-186.  
 Segel GB. Anemia. *Ped in Rev* 1988;10:77-88.  
 Silverstein J. et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care* 2005;28:186-208.

### Infectious Disease and Immunizations

Advisory Committee Statement National Advisory Committee on Immunization. Volume 28. ACS-2.  
 American Academy of Pediatrics. Committee on quality improvement: subcommittee on urinary tract infection. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;103(4pt1):843.  
 American Academy of Pediatrics. Red Book, 28th ed. 2009. Haemophilus influenzae infections: 2009 report of the committee on infectious diseases. p324.  
 American Academy of Pediatrics. Red Book, 28th ed. 2009. Pertussis (whooping cough) 2009 report of the committee on infectious diseases. p504.  
 Baraff LJ, Lee SJ, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* 1993;12:389.  
 Forgie S, Zhanel G, Robinson J. Canadian Paediatric Society Infectious Diseases and Immunization Committee, 2009. Position statement on management of acute otitis media.  
 Public Health Agency of Canada, 2013. Canadian immunization guide.  
 Special Writing Group of the Committee. Rheumatic fever, endocarditis, and Kawasaki disease of the council on cardiovascular disease in the young of the American Heart Association. Guidelines for the diagnosis of rheumatic fever – Jones criteria, 1992 update. *JAMA* 1992;268:2069.

Tiwari T, Murphy TV, Moran J. National Immunization Program, CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *MMWR Recomm Rep* 2005;54(RR-14):1.

Wubbel L, McCracken D, McCracken GH. Management of bacterial meningitis. *Ped in Rev* 1998;19.

Zorc JJ, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. *Clin Microbiol Rev* 2005;18:417.

### Neonatology

Gomella TL, Cunningham MD, Eyal FG, Zenk KE. Neonatology: management, procedures, on-call problems, diseases and drugs, 5th ed. McGraw-Hill, 2004. Assessment of gestational age. pp21-28, 491-6, 559-62.

Jain L and Douglas E. Physiology of fetal lung fluid clearance and the effect of Labor. *Seminars in Perinatology*, 2006.

Joseph J, Zorc ZK. A cyanotic infant: true blue or otherwise? *Pediat Ann* Oct2001;30,10. Research Library. p597

Meinzen-Derr J, Poindexter B, Vrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *J Perinatol* 2009;29:57-62.

Niermeyer S, et al. International guidelines for neonatal resuscitation: an excerpt from the guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: international consensus on science. *Pediatrics* 2000;106:E29.

### Nephrology

Diven SC, Luther BT. A practical primary care approach to hematuria in children. *Pediat Nephrol* 2000;14:65-72.

Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation Conference on proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). *Pediatrics* 2000;105:1242-1249.

Michael RS. Toilet training. *Pediat in Rev* 1999;20.

### Neurology

Bergman I, Painter MJ. Nelson's essentials of pediatrics. 4th ed. W.B. Saunders, 2002. Neurology. p767-820.

Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluation a first nonfebrile seizure in children. Report of the quality standards subcommittee of the American Epilepsy Academy of Neurology. The Child Neurology Society and The American Epilepsy Society. *Neurology* 2000;55:616-623.

Levy RG, Cooper PP. Ketogenic diet for epilepsy. *Cochrane DB Syst Rev* 2003, Issue 3.

Lewis DW, Ashawal S, Dahl G, et al. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Practice parameter: evaluation of children and adolescents with recurrent headaches. *Neurology* 2002;59:490-498.

Lewis, D et al. American Academy of Neurology. Practice parameter: pharmacological treatment of migraine headache in Children and adolescents. *Neurology*. 2004; 63:2215-24.

Tenenbaum S. Clinical neurology and neurosurgery. Elsevier, November 2007. Disseminated encephalomyelitis in children.

### Pharmacology

Hospital for Sick Children. Formulary of infant and enteral formulas. February 2006.

Kowalczyk A. (Ed.). The 2004-2005 formulary: Hospital for Sick Children. Toronto: The Graphic Centre, HSC.

### Respirology

Canadian cystic fibrosis patient data registry report. Canadian Cystic Fibrosis Foundation, 2008.

Gadomski AM, Brower M. Bronchodilators for bronchiolitis. *Cochrane DB Syst Rev* 2010;12:CD001266.

Garrison MM, Christakis DA, Harvey E, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: a meta-analysis. *Pediatrics* 2000;105:e44.

Jain L, Dudell G. Respiratory transition in infants delivered by cesarean section. *Seminars in Perinatology*, 2006.

Lougheed, et al. Canadian Thoracic Society Asthma Management Continuum: 2010 consensus summary for children six yr of age and over, and adults. *Can J Respirol* 2010;17:15-24.

Summary of recommendations from the Canadian Asthma Consensus Guidelines, 2003 and Canadian Pediatric Asthma Consensus Guidelines, 2003 (updated to December 2004) *CMAJ* 2005;173(suppl):S1-56.

### Rheumatology

Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004;110:2747-71.

Olson JC. Nelson's essentials of pediatrics, 3rd ed. WB Saunders, 1998. Rheumatic diseases of childhood. p299-314.

Schneider R. Pinpointing the cause of limb pain in children. *Pediatrics* 1993;576-83.

Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006;43:1089.

### Web-based Resources

Available from: <http://www.medscape.com/home/topics/pediatrics>.

Available from: <http://www.icndata.com/health/pedbase>.

Available from: <http://www.cda-adc.ca>.

Available from: <http://www.aboutkidshealth.ca>.

Available from: <http://www.healthychildren.org>.

Available from: <http://www.publichealth.gc.ca>.

Stephanie Dreckmann and Sangita Sequeira, chapter editors

Jieun Kim and Daniel Soong, associate editors

Jeff Martin, EBM editor

Dr. Melinda Musgrave, staff editor

<b>Acronyms</b> .....	<b>2</b>	<b>Hand</b> .....	<b>22</b>
<b>Basic Anatomy Review</b> .....	<b>2</b>	Traumatic Hand	
Skin		General Management	
Hand		Hand Infections	
Brachial Plexus		Amputations	
Face		Tendons	
<b>Skin Lesions and Masses</b> .....	<b>5</b>	Fractures and Dislocations	
DDx of Skin Lesions/Masses		Dupuytren's Disease	
Surgical Management of Malignant Skin Lesions		Carpal Tunnel Syndrome	
<b>Basic Surgical Techniques</b> .....	<b>6</b>	Rheumatoid Hand	
Sutures and Suturing		<b>Brachial Plexus</b> .....	<b>28</b>
Excision		<b>Craniofacial Injuries</b> .....	<b>28</b>
Skin Biopsy Types and Techniques		Approach to Facial Injuries	
<b>Wounds</b> .....	<b>8</b>	Mandibular Fractures	
Causal Conditions		Maxillary Fractures	
Principles of Wound Healing		Nasal Fractures	
Contaminated and Infected Wounds		Naso-orbital Ethmoid Fractures	
Dressings		Zygomatic Fractures	
Reconstruction		Orbital Floor Fractures	
<b>Soft Tissue Infections</b> .....	<b>14</b>	<b>Breast Surgery</b> .....	<b>32</b>
Erysipelas		Breast Reconstruction	
Cellulitis		Breast Tissue Expanders	
Necrotizing Fasciitis		Breast Reduction	
<b>Ulcers</b> .....	<b>15</b>	<b>Aesthetic Surgery</b> .....	<b>33</b>
Lower Limb Ulcers		Aesthetic Procedures	
Pressure Ulcers		<b>Pediatric Plastic Surgery</b> .....	<b>34</b>
<b>Burns</b> .....	<b>16</b>	Craniofacial Anomalies	
Burn Injuries		Congenital Hand Anomalies	
Pathophysiology of Burn Wounds		<b>References</b> .....	<b>35</b>
Diagnosis and Prognosis			
Indications for Transfer to Burn Centre			
Acute Care of Burn Patients			
Special Considerations			

## Acronyms

ABI	ankle-brachial index	FTSG	full thickness skin graft	PVD	peripheral vascular disease
APL	abductor pollicis longus	GBS	group B <i>Streptococcus</i>	RA	rheumatoid arthritis
ATLS	advanced trauma life support	HTN	hypertension	RL	Ringer's lactate
BMIR	basal metabolic rate	I&D	incision and drainage	ROM	range of motion
CMC	carpo-metacarpal	ICP	intracranial pressure	SGAP	superior gluteal artery perforator
CSF	cerebrospinal fluid	IGAP	inferior gluteal artery perforator	SIADH	syndrome of inappropriate antidiuretic hormone
CVD	cerebrovascular disease	IP	interphalangeal	SIEA	superficial inferior epigastric artery
D5W	5% dextrose in water	MC	metacarpal	SLP	speech language pathology
DIEP	deep inferior epigastric perforator	MCP	metacarpal phalangeal joint	SOF	superior orbital fissure
DIP	distal interphalangeal joint	NCV	nerve conduction velocity	STSG	split thickness skin graft
DM	diabetes mellitus	NS	normal saline	TBSA	total body surface area
EMG	electromyography	NSAIDs	nonsteroidal anti-inflammatory drugs	TMJ	temporomandibular joint
ENT	ear, nose, throat	OM	otitis media	TRAM	transverse rectus abdominus myocutaneous
EOM	extraocular movement	ORIF	open reduction internal fixation	UCL	ulnar collateral ligament
EPB	extensor pollicis brevis	PIP	proximal interphalangeal joint	UV	ultraviolet

## Basic Anatomy Review

### Skin

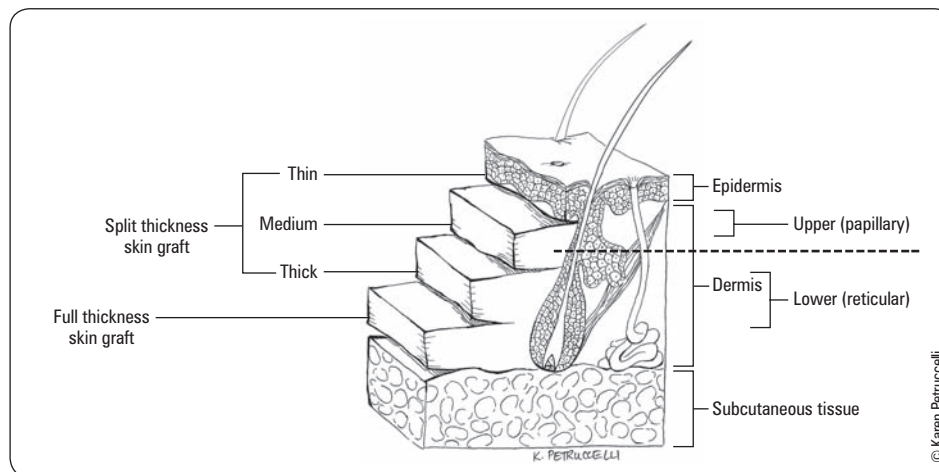


Figure 1. Split and full (whole) thickness skin grafts

### Hand

#### BONES AND NERVES

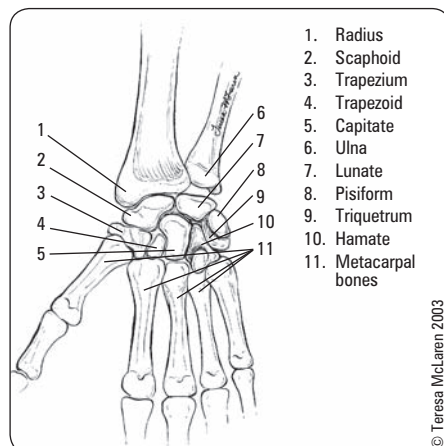


Figure 2. Carpal bones

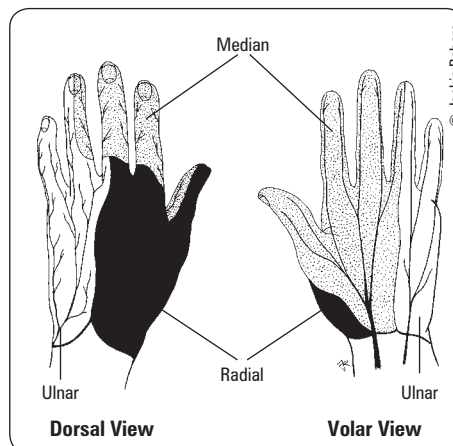


Figure 3. Sensory distribution in the hand

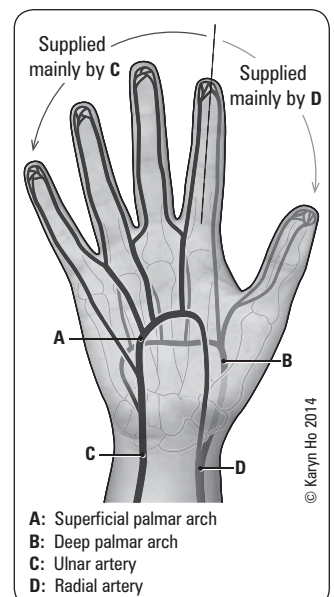


Figure 4. Arterial supply in the hand

## TENDONS

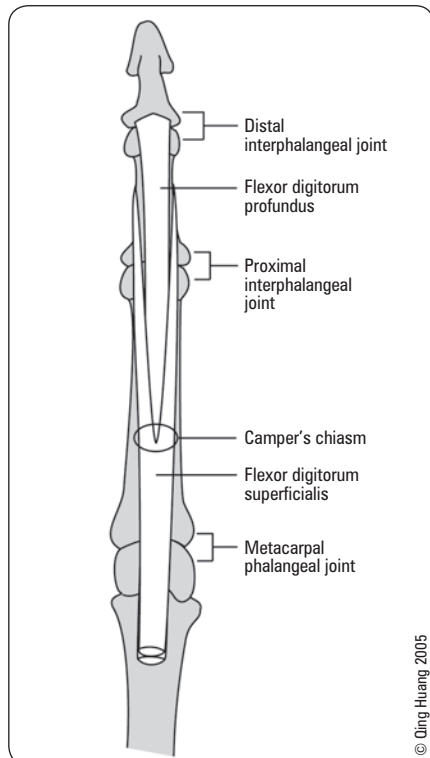


Figure 5. Flexor tendon insertion at PIP and DIP

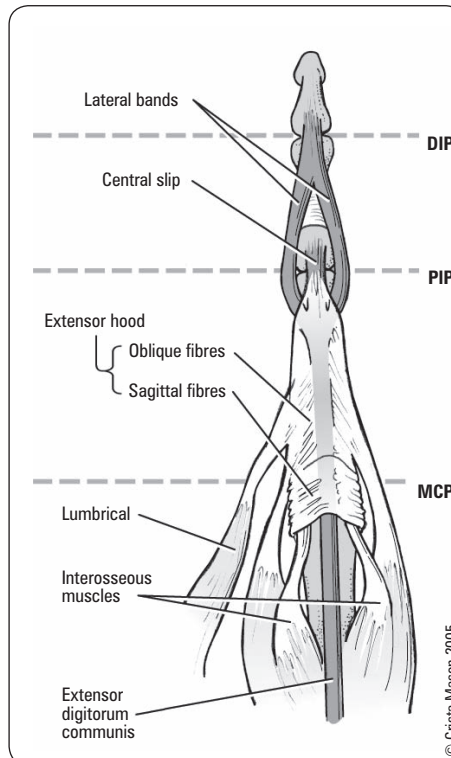


Figure 6. Extensor mechanism of digits



## Carpal Bone Mnemonic

So	Scaphoid
Long	Lunate
To	Triquetrum
Pinky	Pisiform
Here	Hamate
Comes	Capitate
The	Trapezoid
Thumb	Trapezium



## Flexor Tendons

All require OR repair.

## Extensor Tendons

ER repair unless proximal/multiple tendons.

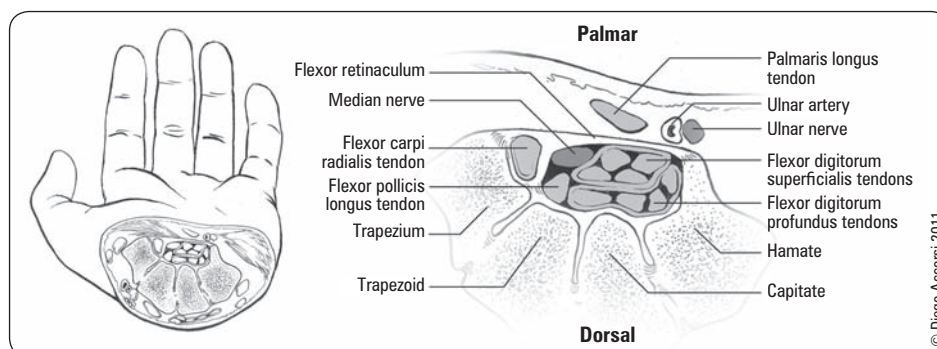


Figure 7. Carpal tunnel

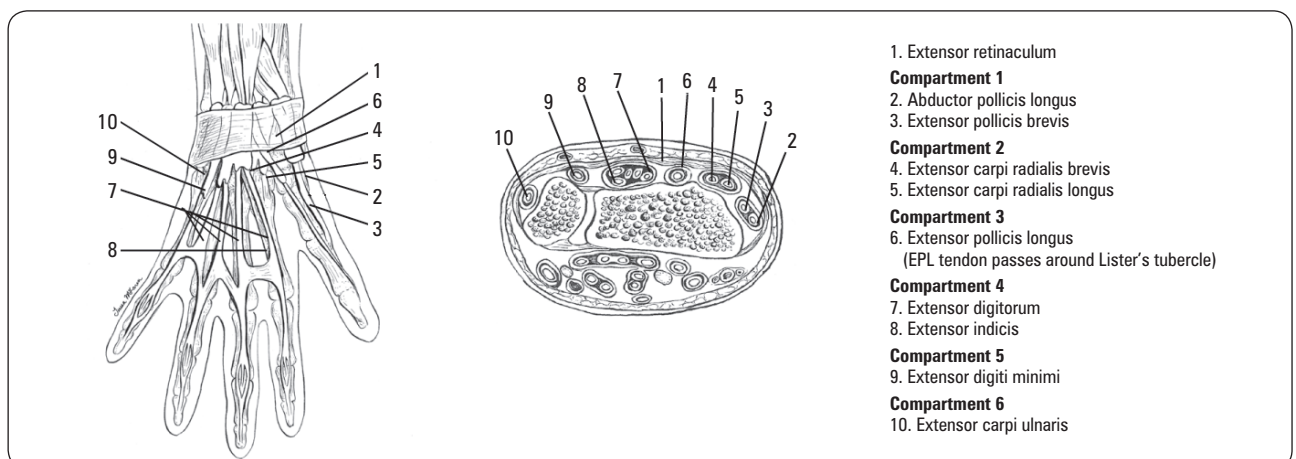
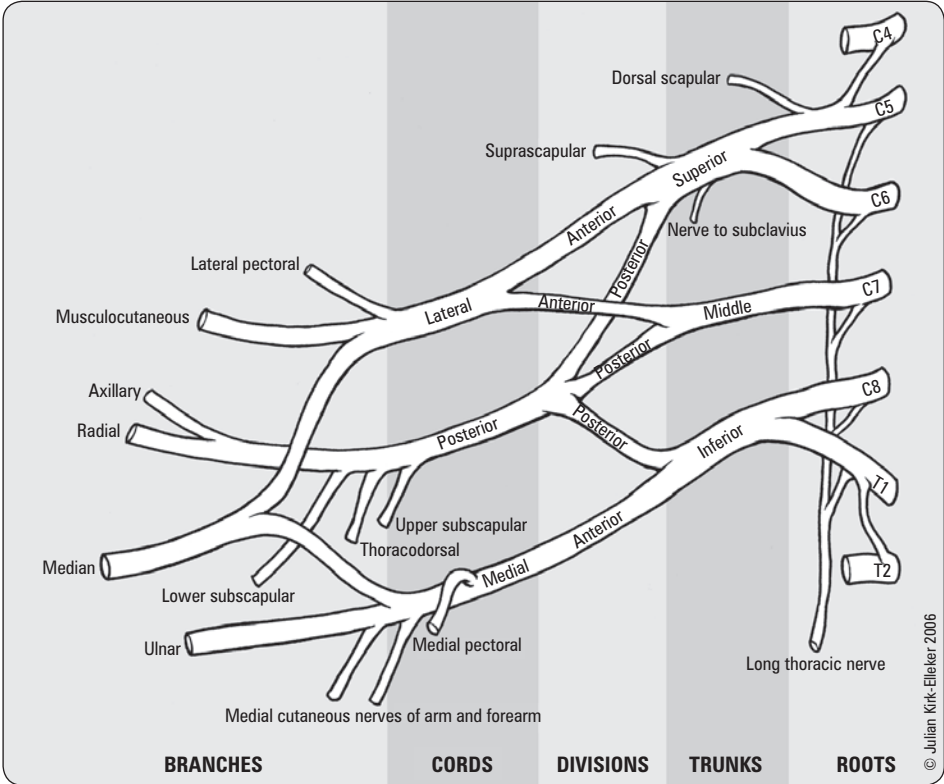


Figure 8. Extensor compartments of the wrist (dorsal view and cross-sectional view)

Brachial Plexus



**Brachial Plexus Mnemonic**  
Rob – Roots  
Thomas – Trunks  
Drinks – Divisions  
Cold – Cords  
Beers – Branches

Figure 9. Brachial plexus anatomy

Face

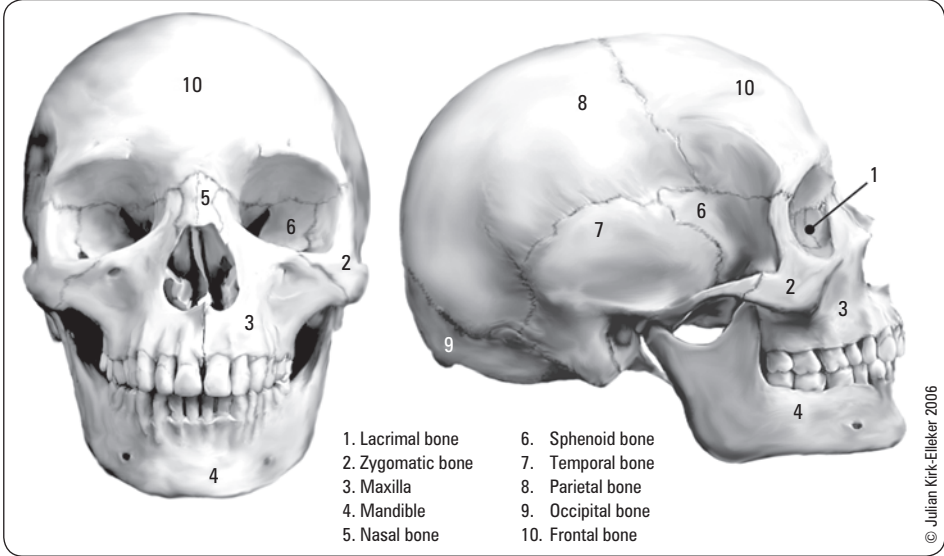


Figure 10. Skull and facial bones



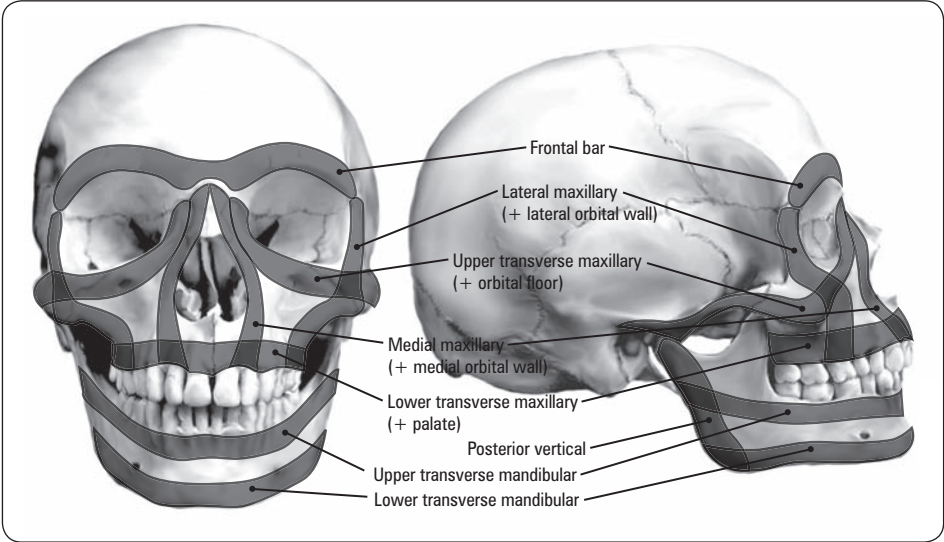


Figure 11. Craniofacial horizontal and vertical buttresses

**Skin Lesions and Masses**



**DDx of Skin Lesions/Masses**

- for background information and medical management, see [Dermatology](#)
- for biopsy techniques, see PL7



**Surgical Management of Malignant Skin Lesions**

- surgical treatment for all malignant skin lesions involve total excision of the primary lesion
- excision margin of lesion depends on the diameter and depth
- for decisions regarding reconstruction using flaps or skin grafts, see *Reconstruction*, PL11

**Precursors of Malignant Lesions**

Table 1. Precursors

Basal Cell Carcinoma	Squamous Cell Carcinoma	Malignant Melanoma
No known precursor	Actinic keratosis Bowen's disease Bowenoid papulosis Paget's disease Leukoplakia Erythroplasia	Dysplastic nevus Lentigo maligna Giant congenital nevus

**Surgical Margins**

Table 2. Surgical Margins for Basal Cell Carcinoma

Diameter of Lesion	Surgical Margins
2 cm or less	3 mm
>2 cm	5 mm

Table 3. Surgical Margins for Squamous Cell Carcinoma

Diameter or Location of Lesion	Surgical Margins
2 cm or less*	4 mm*
>2 cm	6 mm
High risk (facial)	6 mm
Low risk (elsewhere)	4 mm

\*For a high risk lesion that is <2 cm in diameter, use a 6 mm margin

**Table 4. Surgical Margins for Malignant Melanoma**

Depth of Lesion	Surgical Margins
In situ	0.5 cm
<1 mm	1 cm
1.01-1.99 mm	1-2 cm
≥2 mm	2 cm



Traumatic tattoos are permanent discolorations resulting from new skin growth over foreign material or dirt left behind in the dermis. Copious irrigation should be done ASAP.

## Basic Surgical Techniques

### Sutures and Suturing

#### ANESTHESIA

- debride and irrigate before injecting anesthetic
- toxicity of mixtures (i.e. lidocaine + bupivacaine) is no greater than its individual components

**Table 5. Toxic Limit and Duration of action (1 cc of 1% solution contains 10 mg lidocaine)**

	Without Epinephrine	With Epinephrine (vasoconstrictor, limits bleeding)
Lidocaine (Xylocaine®)	5 mg/kg, lasts 45-60 min	7 mg/kg, lasts 2-6 h
Bupivacaine (Marcaine®) for longer analgesic effect	2 mg/kg, lasts 2-4 h	3 mg/kg, lasts 3-7 h

#### IRRIGATION AND DEBRIDEMENT

- irrigate copiously with a physiologic solution such as Ringer's lactate or normal saline to remove surface clots, foreign material, and bacteria
- debride all obviously devitalized tissue, irregular or ragged wounds must be excised to produce sharp wound edges that will assist healing when approximated

#### SUTURES

- use of a particular suture material is highly dependent on surgeon preference. However, skin should be closed with a non absorbable when trauma
- suture material divided by two categories (see Table 6)

**Table 6. Suture Materials: Absorbable vs. Non-absorbable and Monofilament vs. Multifilament**

Suture Materials	Uses	Examples	Notes
Absorbable	Deep sutures under short-term tension Skin closure in children	Plain gut®, Vicryl®, Polysorb®	loses at least 50% of their strength in 4 wk; eventually absorbed
Non-absorbable	Skin closure Sites of long term tension	Nylon, polypropylene, stainless steel	Lower likelihood of wound dehiscence
Monofilament	Contaminated and infected wounds (lower likelihood of bacterial trapping in suture material)	Monosof®, Monocryl®, Biosyn®	Slides through tissue with less friction; more memory/stiffness
Multifilament	AVOID in contaminated wounds (increased likelihood of bacterial trapping)	Vicryl® and Silk	Less memory/stiffness thus easier to work with

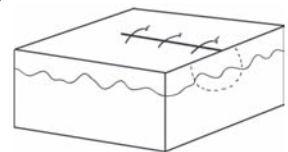
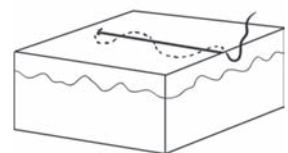
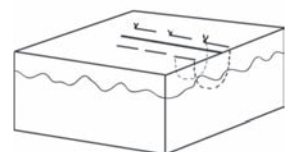
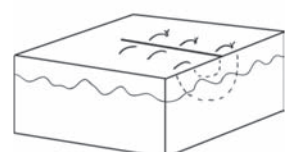
### BASIC SUTURING TECHNIQUES

#### Basic Suture Methods (Figure 12)

- simple interrupted: can be used in almost all situations
- sub-cuticular: good cosmetic result but weak, used in combination with deep sutures; not used in trauma
- vertical mattress: for areas difficult to evert (e.g. dorsum of the hand)
- horizontal mattress: everting, time saving
- continuous over and over (aka "running", "baseball stitch"): time saving, good for hemostasis

#### Basic Principles

- minimize tissue trauma: follow curve of needle, handle wound edges gently (use toothed forceps), use just enough tension to approximate edges (do not strangulate)
- use the finest needle and suture possible
- ensure good cosmesis (see sidebar)

**Simple Interrupted****Sub-cuticular****Horizontal Mattress****Vertical Mattress****Deep Dermal**

© Baseer Khan, Tabby Lutham 2010

**Figure 12. Basic suture methods**

#### Steps to Ensuring Good Suturing Cosmesis:

- Incisions should be made along relaxed skin tension lines
- Attain close apposition of wound edges
- Minimize tension on skin by closing in layers
- Evert wound edges
- Use appropriately sized suture for skin closure (5-0, 6-0 on face; 3-0, 4-0 elsewhere)
- Ensure equal width and depth of tissue on both sides
- Remove sutures within 5-7 d from the face, 10-14 d from scalp/torso/ extremities

### Other Skin Closure Materials

- tapes: may be indicated for superficial wounds and those with opposable edges. Tape cannot be used on actively bleeding wounds. When placed across the incision, will prevent surface marks and can be used primarily or after surface sutures have been removed. Tape burns may occur if there is excessive tension or swelling around the incision
- skin adhesives: e.g. 2-octylcyanoacrylate (e.g. Dermabond®) works well on small areas without much tension or shearing. May cause irreversible tattooing
- staples: steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture)

## Excision

- incise along relaxed skin tension lines to minimize appearance of scar (Figure 13)
- use elliptical incision to prevent “dog ears” (heaped up skin at end of incision)
- if needed, undermine skin edges to decrease wound tension
- use layered closure including dermal sutures when wound is deeper than superficial (decreases tension)

## Skin Biopsy Types and Techniques

### SHAVE BIOPSY

- used for superficial lesions where sampling of the full thickness of the dermis is not necessary
- most suitable lesions for shave biopsies are either elevated above the skin or have pathology confined to the epidermis (e.g. seborrheic or actinic keratoses, skin tags, warts, and superficial basal cell or squamous cell carcinomas)
- rapid, requires little training, and does not require sutures for closure
- should not be used for pigmented lesions – an unsuspected melanoma cannot be properly staged if partially removed

### PUNCH BIOPSY

- involves the removal of a core-shaped piece of tissue, performed with round, disposable knives ranging in diameter from 2 to 10 mm
- allows sampling of the deep dermis
- can be used for the diagnosis and treatment of small pigmented lesions and atypical moles
- punch biopsy wounds can be closed with suture or left to heal by secondary intention. Punches greater than 3 mm may produce scarring and are best closed with one or two sutures
- has low incidence of infection, bleeding, nonhealing, significant scarring

### EXCISIONAL BIOPSY

- performed for lesions that require complete removal for diagnostic or therapeutic purposes
- performed for lesions that cannot be adequately punch biopsied due to size, depth, or location
- requires the greatest amount of expertise and time
- always requires sutures for closure

### TECHNIQUE

#### General

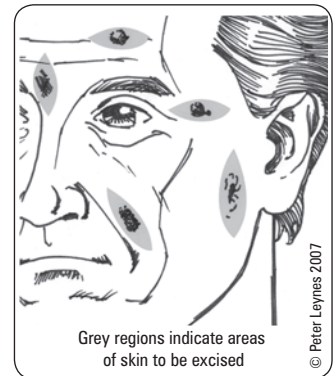
- all biopsies performed in clinic are done using aseptic technique, but are not sterile
- sterile gloves are indicated for biopsies and excisions in all patients

#### Preparing the Site

- common skin antiseptics (betadine, chlorhexidine) can be used to prepare the biopsy site
- chlorhexidine is used in concentrations ranging from 0.5-4%. This higher concentration cannot be used on the face as it could get into the eyes and may burn or cause damage
- mark the intended lesion and surgical margins with a surgical marker since they may be temporarily obliterated following injection of the anesthetic
- for all biopsies, a sterile drape technique is indicated. A fenestrated surgical drape is placed around the biopsy site after the area is cleansed and anesthetized

#### Anesthesia

- most commonly used local anesthetic is 1% or 2% lidocaine
- small amounts of epinephrine are added to constrict blood vessels, decrease bleeding, prolong anesthesia, and limit lidocaine toxicity. The local with epinephrine can be injected directly into the lesion
- local anesthetics with epinephrine may be used anywhere in the body including the digits
- epinephrine should be avoided in patients with history of vascular compromise
- a field block should be performed for larger lesions by placing a ring of anesthetic around the surgical site, advancing and injecting through a site that has been previously anesthetized



**Figure 13. Incision of lesions along relaxed skin tension lines**



#### Relaxed Skin Tension Lines

Natural skin/wrinkle lines with minimal linear tension. Placing incisions parallel to relaxed skin tension lines minimizes widening/hypertrophy, and helps to camouflage scars.

# Wounds



## Causal Conditions

- laceration: cut or torn tissue
- abrasion: superficial skin layer is removed, variable depth
- contusion: injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact yet injured
- avulsion: tissue/limb forcefully separated from surrounding tissue, either partially or fully; “de-gloving”
- puncture wounds: opening relatively small as compared with depth (e.g. needle)
  - includes bite wounds
- crush injuries: caused by compression
- thermal and chemical wounds

## Principles of Wound Healing

- wound: disruption of the normal anatomical relationships of tissue as a result of injury

### STAGES OF WOUND HEALING

- see Figure 14
- growth factors released by tissues play an important role
- scar is mature once it has completed the final stage



### FACTORS INFLUENCING WOUND HEALING

#### Local (reversible/controllable):

- mechanical (local trauma, tension)
- blood supply (ischemia/circulation)
- temperature
- technique and suture materials
- retained foreign body
- infection
- hematoma/seroma (↑ infection rate)
- venous hypertension
- peripheral vascular disease

#### General (often irreversible):

- age
- nutrition (protein, vitamin C, O<sub>2</sub>)
- smoking
- chronic illness (e.g. diabetes, cancer, CVD)
- immunosuppression (steroids, chemo, radiation)
- collagen vascular disease
- tissue irradiation



Myofibroblasts are the cells responsible for wound contraction. They do this at a rate of less than 0.75 mm/d.

PHASE	PROCESS
<b>1. Inflammatory Phase (Reactive) (Days 1-6)</b> <ul style="list-style-type: none"> <li>• Limits damage, prevents further injury</li> <li>• Debris and organisms cleared via inflammatory response:               <ul style="list-style-type: none"> <li>• Neutrophils (24-48 h)</li> <li>• Macrophages: critical to wound healing by orchestrating growth factors for collagen production (48-96 h)</li> <li>• Lymphocytes: role poorly defined (5-7 d)</li> </ul> </li> </ul>	→ <ol style="list-style-type: none"> <li>1. Hemostasis – vasoconstriction + platelet plug</li> <li>2. Chemotaxis – migration of macrophages and PMN</li> </ol>
<b>2. Proliferative Phase (Regenerative) (Day 4 – Week 3)</b> <ul style="list-style-type: none"> <li>• Fibroblasts attracted and activated by macrophage growth factors</li> <li>• Reparative process: re-epithelialisation, matrix synthesis, angiogenesis (relieves ischemia)</li> <li>• Tensile strength begins to increase at days 4-5</li> </ul>	→ <ol style="list-style-type: none"> <li>1. Collagen synthesis (mainly type III)</li> <li>2. Angiogenesis</li> <li>3. Epithelialization</li> </ol>
<b>3. Remodeling Phase (Maturation) (Week 3 – 1 year)</b> <ul style="list-style-type: none"> <li>• Increasing collagen organization and stronger crosslinks</li> <li>• Type I collagen replaces Type III until normal 4:1 ratio achieved</li> <li>• Peak tensile strength at 60 d – 80% of preinjury strength</li> </ul>	→ <ol style="list-style-type: none"> <li>1. Contraction</li> <li>2. Scarring</li> <li>3. Remodeling of scar</li> </ol>

Figure 14. Stages of wound healing

## ABNORMAL HEALING

### Hypertrophic Scar

- scar remains roughly within boundaries of original injury
- red, raised, widened, frequently pruritic
- common sites: back, shoulder, sternum
- treatment: pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur), typically improves with time

### Keloid Scar

- scar extends beyond boundaries of original injury
- frequently pruritic, often painful; collagen in whorls rather than bundles
- common sites: sternum, deltoid, earlobe; more common in darker skinned people
- treatment: pressure garments, silicone gel sheeting, corticosteroid injection, radiation therapy ± surgical excision as a last resort

### Chronic Wound

- fails to heal primarily within 4-6 wk
- common chronic wounds include diabetic, pressure and venous stasis ulcers
- treatment: may heal with meticulous wound care; may also require surgical intervention
- Marjolin's ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation → consider biopsy of chronic wound

## WOUND CLOSURE

### Primary (1°) Closure (First Intention)

- definition: wound closure by direct approximation of edges within hours of wound creation (i.e. with sutures, staples, skin graft, etc.)
- indication: recent (<6 h, longer with facial wounds), clean wounds
- contraindications: animal/human bites (except on face), crush injuries, infection, long time lapse since injury (>6-8 h), retained foreign body

### Secondary (2°) Closure/Spontaneous Healing (Second Intention)

- definition: wound left open to heal spontaneously (epithelialization 1 mm/d from wound margins in concentric pattern), contraction (myofibroblasts) and granulation – maintained in inflammatory phase until wound closed; requires dressing changes; inferior cosmetic result
- indication: when 1° closure not possible or indicated (see *Primary Closure*, above)

### Tertiary (3°) Closure/Delayed Primary Closure (Third Intention)

- definition: intentionally interrupt healing process (e.g. with packing), then wound can be closed at 4-10 d post-injury after granulation tissue has formed and there is <10<sup>5</sup> bacteria/gram of tissue
- indication: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization
- prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

## Contaminated and Infected Wounds

### Definitions

- contamination: the presence of non-replicating microorganisms within a wound
- colonization: the presence of replicating microorganisms within a wound
- infection: greater than 10<sup>5</sup> microorganisms in a wound without intact epithelium, a wound may also be infected with small amounts of a very virulent organism (e.g. GBS)

### Management of Acute Contaminated Wound (<24 h)

- cleanse and irrigate open wound with physiologic solution (NS or RL)
- evaluate for injury to underlying structures (vessels, nerve, tendon and bone)
- control active bleeding
- debridement: removal of foreign material, devitalized tissue, old blood
  - surgical debridement: blade and irrigation if indicated
- systemic antibiotics are commonly indicated for obvious infection, wound older than 8 h, severely contaminated, immunocompromised, involvement of deeper structures (e.g. joints, fractures)
- ± tetanus toxoid 0.5 mL IM ± tetanus immunoglobulin 250 U deep IM (see Table 7 and Table 8)
- ± post-exposure treatment of
  - hepatitis B, HIV, hepatitis C (if titres confirmed at 6 mo)



#### Risk Factors for Infection

- Virulence of the infecting microorganism
- Amount of bacteria present
- Host resistance

- re-evaluate in 24-48 h for signs of deep infection
  - open infected portion of wound by removing sutures if evidence of infection (i.e. erythema, warmth, pain, discharge)

**Table 7. Risks for Tetanus**

Wound Characteristics	Tetanus-Prone	Not Tetanus-Prone
Time since injury	> 6 h	< 6 h
Depth of injury	> 1 cm	< 1 cm
Mechanism of Injury	Crush, burn, gunshot, frostbite, puncture through clothing, farming injury	Sharp cut (e.g. clean knife, clean glass)
Devitalized tissue	Present	Not present
Contamination (e.g. soil, dirt, saliva, grass)	Yes	No
Retained foreign body	Yes	No

**Table 8. Tetanus Immunization Recommendations**

History of Tetanus Immunization	Clean, Minor Wounds		All Other Wounds	
	Td or Tdap*	Tig**	Td or Tdap	Tig
Uncertain or <3 doses of immunization	Yes	No	Yes	Yes
3 doses received in immunization series	No~	No	No§	No¶

\* 0.5 mL of combined tetanus and diphtheria toxoids ± acellular pertussis

\*\* Tetanus immune globulin, 250 U given at a separate site from Td/Tdap

~ Yes, if >10 yr since last booster

§ Yes, if >5 yr since last booster

¶ Yes, if immunocompromised

### Management of Contaminated Wounds (>24 h, including ulcers)

- irrigation and debridement
  - traumatic tattooing can occur if foreign materials left in wound
- systemic antibiotics indicated if there is concern of infection (e.g. redness, swelling, pain, clinically unwell)
- topical antimicrobials: beneficial for minor wounds, but no additional benefit for wounds requiring systemic antibiotics. May aid in healing of chronic wounds
- closure: final closure via secondary intention (most common), delayed wound closure (3° closure), skin graft or flap; successful closure depends on bacterial count of  $\leq 10^5/\text{cm}^3$  prior to closure and frequent dressing changes

### BITES

- see [Emergency Medicine](#), ER46



### Dog and Cat Bites

- pathogens: *Pasteurella multocida*, *S. aureus*, *S. viridans*
- investigations: same as for human bites; see below
- treatment: Clavulin® (500 mg PO q8h started immediately – amoxicillin + clavulanic acid)
  - consider rabies prophylaxis if animal has symptoms of rabies or unknown animal
    - ♦ ± rabies Ig (20 IU/kg around wound, or IM) and 1 of the 3 types of rabies vaccines (1.0 mL IM in deltoid, repeat on days 3, 7, 14, 28)
  - aggressive irrigation with debridement
  - healing by secondary intention is mainstay of treatment
  - only consider primary closure for bite wounds on the face; otherwise primary closure is contraindicated
  - contact Public Health if animal status unknown

### Human Bites

- pathogens: *Staphylococcus* >  $\alpha$ -hemolytic *Streptococcus* > *Eikenella corrodens* > *Bacteroides*
- mechanism: most commonly over dorsum of MCP from a punch in mouth; “fight-bite”
- serious, as mouth has  $10^9$  microorganisms/mL, which get trapped in joint space when fist unclenches and overlying skin forms an air-tight covering ideal for anaerobic growth – can lead to septic arthritis
- investigations:
  - radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  - culture for aerobic and anaerobic organisms, Gram stain
- treatment:
  - urgent surgical exploration of joint, drainage and debridement of infected tissue
  - wound must be copiously irrigated
  - Clavulin® 500 mg PO q8h, clindamycin 300 mg PO q6h + ciprofloxacin 500 mg PO q12h (if allergic to penicillin) + secondary closure
  - splint



## Dressings

- there is no one dressing for any given type of wound. Dressing selection depends on the wound characteristics
  - as the wound progresses through healing it will require different types of dressings, therefore, routine inspection is recommended
  - principles of dressings:
    - ♦ moist vs. dry wounds (see Table 9)
      - purpose of dressings should be to keep wound appropriately moist (i.e. moistening dry wounds or removing excess exudate/blood from wet wounds)
    - ♦ clean vs. infected wounds
      - clean wounds can be dressed with petroleum based gauze, which is non-adhering to epithelializing tissue; requires secondary dressing
      - infected wounds can be dressed with iodine gauze, silver-containing, or antimicrobial dressings
    - ♦ wide-based vs. cavitary/tunneling wounds
      - cavitary or tunnelling wounds (i.e. through a fascial layer) can be packed with saline-soaked (non-infected), betadine-soaked (infected) ribbon gauze, or other easily retrievable one-piece moisture providing dressing

**Table 9. Recommended Dressings for Wound Type**

Wound Depth	Exudate Level	Dressing Material
<b>Superficial</b>	Lightly exuding	Films (Opsite®), hydrogels (Intrasite®, Nu-gel®, Duoderm®)
	Any exudate level	Contact layers
<b>Superficial to Deep</b>	Light to moderately exuding wounds	Amorphous gels, hydrogels, hydrocolloids (Duoderm®, Tegaderm®), collagen, hypertonic saline gauze (Mesalt®)
	Moderately to heavily exuding wounds	Foams (Mepilex®, Allevyn®), alginates (Sorbsan®, Kaltostat®), hypertonic saline gauze, hydrofibre (Aquacel®)

Table adapted from Grabb & Smith's Plastic Surgery 6th Edition Chapter 3, Table 3.3

## Reconstruction

### SKIN GRAFTS

#### Definition

- skin that is harvested from a donor site and transferred to the recipient site and that does not carry its own blood supply. Survival requires the generation of new blood vessels from the recipient site bed. They are classified according to the depth of dermis they contain: full thickness (entire epidermis + dermis) vs. split-thickness (epidermis + partial dermis)

#### Donor Site Selection

- must consider size, hair pattern, texture, thickness of skin, and colour (facial grafts best if taken from “blush zones” above clavicle e.g. pre/post auricular or neck)
- partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)

#### Partial Thickness Skin Graft Survival

- 3 phases of skin graft “take”
  1. plasmatic imbibition: diffusion of nutrition from recipient site (first 48 h)
  2. inosculation: vessels in graft connect with those in recipient bed (day 2-3)
  3. neovascular ingrowth: graft revascularized (day 3-5)
- requirements for survival
  - bed: well-vascularized (unsuitable: bone, tendon, heavily irradiated, infected wounds, etc.)
  - contact between graft and recipient bed: fully immobile (decreased shearing and hematoma formation)
  - staples, sutures, splinting, and appropriate dressings (pressure) are used to prevent movement of graft and hematoma or seroma formation
  - site: low bacterial count ( $<10^5/\text{cm}^3$ , to prevent infection)

#### Classification of Skin Grafts

1. by species
  - autograft: from same individual
  - allograft (homograft): from same species, different individual
  - xenograft (heterograft): from different species (e.g. porcine)
2. by thickness: see Table 10



#### Reconstruction Ladder (in the order of increasing complexity of treatment)

- Dressings
- Primary closure
- Delayed closure
- Split thickness graft
- Full thickness graft
- Tissue expansion
- Random pattern flap
- Pedicle flap
- Free flap

Table 10. Skin Grafts

	Split Thickness Skin Graft	Full Thickness Skin Graft
<b>Definition</b>	Epidermis and part of dermis	Epidermis and all of dermis
<b>Donor Site</b>	More sites	Limited donor sites (full thickness skin loss, must be closed 1° or with STSG)
<b>Healing of Donor Site</b>	Re-epithelialization via dermal appendages in graft and wound edges	Primary closure
<b>Re-harvesting</b>	~10 d (faster on scalp)	N/A
<b>Graft Take</b>	Easier; shorter nutrient diffusion distance	Lower rate of survival (thicker, slower vascularization)
<b>Contraction</b>	Less 1° contraction, greater 2° contraction (less with thicker graft)	Greater 1° contraction, less 2° contraction
<b>Aesthetic</b>	Poor	Good
<b>Comments</b>	Can be meshed for greater area (see below) Allows for extravasation of blood/serum	May use on face and fingers
<b>Advantage</b>	Takes well in less favourable conditions, can cover a larger area	Resists contraction, texture/pigment more normal
<b>Disadvantage</b>	Contracts significantly, abnormal pigmentation, high susceptibility to trauma	Requires well vascularized bed Must remove fat from graft before application
<b>Uses</b>	Large areas of skin, granulating tissue beds	Face (colour match), site where thick skin or decreased contracture is desired (e.g. finger)

**Graft Contraction**

- Primary: immediate reduction in size upon harvesting
- Secondary: reduction in size once graft placed on wound bed

- mesh graft
  - **advantages**
    - ♦ prevents accumulation of fluids (e.g. hematoma, seroma)
    - ♦ covers a larger area
    - ♦ best for contaminated recipient site
  - **disadvantages**
    - ♦ poor cosmesis (“alligator hide” appearance)
    - ♦ has significant contractures
- common reasons for graft loss: hematoma/seroma, infection, mechanical force (e.g. shearing, pressure)

**OTHER GRAFTS**

Table 11. Various Tissue Grafts

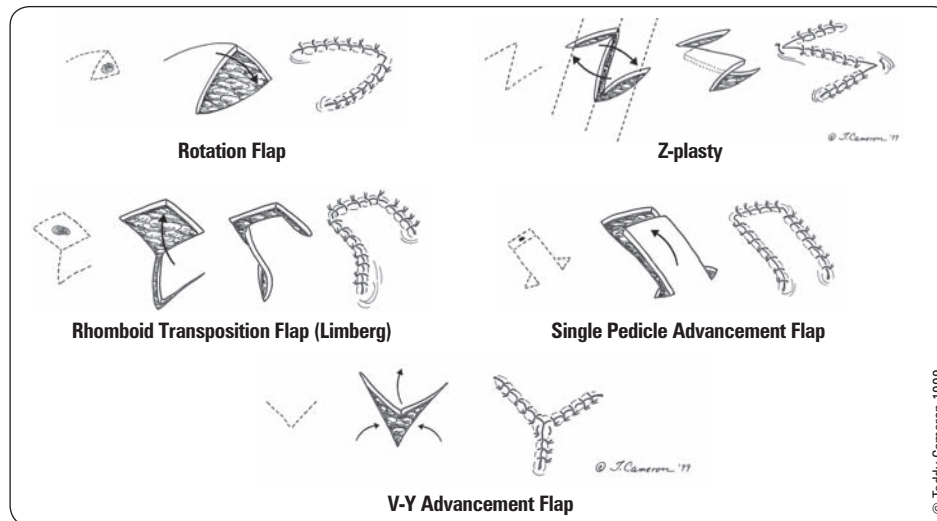
Graft Type	Use	Preferred Donor Site
<b>Bone</b>	Repair rigid defects	Cranial, rib, iliac, fibula
<b>Cartilage</b>	Restore contour of ear and nose	Ear, nasal septum, costal cartilage
<b>Tendon</b>	Repair damaged tendon	Palmaris longus, plantaris
<b>Nerve</b>	Conduit for regeneration across nerve gap	Sural, antebrachial cutaneous, medial brachial cutaneous
<b>Vessel</b>	Bridge vascular gaps	Forearm or foot vessels for small vessels, saphenous vein for larger vessels
<b>Dermis</b>	Contour restoration ( $\pm$ fat for bulk)	Thick skin of buttock or abdomen
<b>Fat</b>	Contour restoration	Abdomen, any area with fat available

**FLAPS**

- **definition:** tissue transferred from one site to another with a known blood supply (random, pedicled or named); not dependent on neovascularization, unlike a graft
- **may consist of:** skin, subcutaneous tissue, fascia, muscle, bone, other tissue (e.g. omentum)
- **classification:** based on blood supply to skin (random, axial) and anatomic location (local, regional, distant)
- **indications for flaps**
  - reconstruction: replaces tissue loss due to trauma or surgery
  - provides skin and temporary soft tissue coverage through which surgery can be carried out later
  - improves blood supply to poorly vascularized bed (e.g. bone)
- **complications:** flap loss due to hematoma, seroma, infection, poor flap design, extrinsic compression (dressing too tight) or vascular failure/thrombosis, fat necrosis (in free flaps)

**Random Pattern Flaps** (see Figure 15)

- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply (typically 2:1)
- flap choice is often a combination of available tissue, location of reconstruction site with respect to donor site, and surgeon preference
- **types**
  - **rotation:** cover wounds of various sizes; common use: sacral pressure sores
  - **transposition:** smaller in size compared to rotation flaps and advancement flaps; commonly used on certain areas of the face using adjacent areas of excess skin laxity
  - **Z-plasty:** used to reorient a scar, lengthen the line of a scar or to break up a scar
  - **advancement flaps (V-Y, Y-V)**
    - ♦ single/bipedicle V-Y flaps: wounds with lax surrounding tissue; the pedicle is the deep tissue underlying the flap

**Figure 15. Wound care flaps – random pattern****Axial Pattern Flaps (Arterialized)**

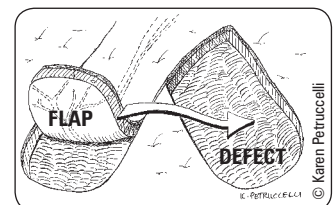
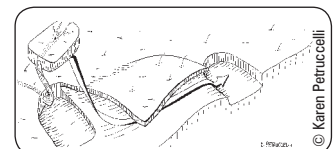
- flap contains a well defined artery and vein
- allows greater length:width ratio (5-6:1)
- **types**
  - **peninsular flap:** skin and vessel intact in pedicle (see Figure 16)
  - **island flap:** vessel intact, pedicle is better defined (see Figure 17)
  - **free flap:** vascular supply anastomosed at recipient site by microsurgical techniques
- can be sub-classified according to tissue content of flap:
  - e.g. musculocutaneous/myocutaneous (e.g. transverse rectus abdominal myocutaneous) vs. fasciocutaneous

**Free Flaps**

- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and veins to a flap and performing a microscopic anastomosis between these and the vessels in the recipient wound
- survival rates >95%
- **types:** muscle and skin (common), bone, jejunum, omentum
  - e.g. radial forearm, scapular, latissimus dorsi

**Table 12. Free Flap Characteristics**

Characteristic	Normal	Arterial Insufficiency	Venous Insufficiency
Colour	Pink	Pale	Purple or blue
Temperature	Warm	Cool	Warm or cool
Arterial Pulse (Doppler)	+	±	±
Turgor	Soft, but with tissue turgor	Decreased	Increased (i.e. tense)

**Figure 16. Peninsular axial pattern flap****Figure 17. Island axial pattern flap**

# Soft Tissue Infections

**Table 13. Classification of Soft Tissue Infections by Depth**

<b>Erysipelas</b>	Superficial with subcutaneous tissue involvement
<b>Cellulitis</b>	Full thickness with subcutaneous tissue involvement
<b>Fasciitis</b>	Fascia
<b>Myositis</b>	Muscle

## Erysipelas

### Definition

- acute skin infection that is more superficial than cellulitis

### Etiology

- typically caused by Group A  $\beta$ -hemolytic *Streptococcus*

### Clinical Features

- intense erythema, induration, and **sharply demarcated borders** (differentiates it from other skin infections)

### Treatment

- penicillin or first generation cephalosporin (e.g. cefazolin or cephalexin)

## Cellulitis

### Definition

- non-suppurative infection of skin and subcutaneous tissues

### Etiology

- skin flora most common organisms: *S. aureus*,  $\beta$ -hemolytic *Streptococcus*
- immunocompromised: Gram-negative rods and fungi

### Clinical Features

- source of infection
  - trauma, recent surgery
  - PVD, diabetes – cracked skin in feet/toes
  - foreign bodies (IV, orthopaedic pins)
- systemic symptoms (fever, chills, malaise)
- pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (visible red streaking in skin proximal to area of cellulitis)

### Investigations

- CBC, blood cultures
- culture and Gram stain wound/aspirate from wound if open wound
- plain radiographs if suspect foreign body or abscess
  - r/o bone invasion (osteomyelitis)

### Treatment

- antibiotics: first line – cephalexin 500 mg PO q6h or cloxacillin 500 mg PO q6h x 7 d; if complicated (e.g. lymphangitis, DM) consider IV cefazolin 1-2 g q8h
- outline area of erythema to monitor success of treatment
- immobilize and splint (hands)



**Cellulitis vs. Erysipelas**  
Cellulitis: indistinct borders  
Erysipelas: sharp borders

## Necrotizing Fasciitis

### Definition

- rapidly spreading, very painful infection of the deep fascia with necrosis of tissues
- some bacteria create gas that can be felt as crepitus and be seen on x-rays
- infection spreads rapidly along deep fascial plane and is **limb and life threatening**

### Etiology

- Type I: polymicrobial (less aggressive)
- Type II: monomicrobial, usually  $\beta$ -hemolytic *Streptococcus*



**Soft tissue infections:** Suspect necrotizing fasciitis with rapidly spreading erythema and edema. **Must demarcate** erythematous area on admission in order to determine amount of spread/rapidity of spread.

### Clinical Features

- **pain out of proportion to clinical findings and beyond border of erythema**, edema, tenderness,  $\pm$  crepitus (subcutaneous gas from anaerobes)  $\pm$  fever
- infection spreads very rapidly
- patients may look deceptively well at first, but may rapidly become very sick/toxic
- late findings:
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of bullae
  - cutaneous gangrene, subcutaneous emphysema

### Investigations

- a **clinical diagnosis**
- CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, myonecrosis, etc.)
- severely elevated CK: usually means myonecrosis (late sign)
- hemostat easily passed along fascial plane; fascial biopsy to rule out in equivocal situations

### Treatment

- rigorous resuscitation (ABCs)
- urgent surgical debridement: remove all necrotic tissue, copious irrigation
- IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4h or clindamycin 900 mg IV q6h until final cultures available
- urgent consultation with infectious disease specialist is recommended

## Ulcers



### Lower Limb Ulcers

#### Traumatic Ulcers (Acute)

- failure of lesions to heal, usually due to compromised blood supply and unstable scar
- usually over bony prominence  $\pm$  edema  $\pm$  pigmentation changes  $\pm$  pain
- treatment: debridement of ulcer and compromised tissue, left to heal via secondary intention with dressings, may need reconstruction with local or distant flap in select cases, vascular status of limb must be assessed clinically and via vascular studies (i.e. sonographically)

#### Non-Traumatic Ulcers (Chronic)

Table 14. Venous vs. Arterial vs. Diabetic Ulcers

Characteristic	Venous (70% vascular ulcers)	Arterial	Diabetic
<b>Cause</b>	Valvular incompetence Venous HTN	2° to small and/or large vessel disease (be aware of risk factors)	Peripheral neuropathy: decreased sensation Atherosclerosis: decreased regional blood flow
<b>History</b>	Dependent edema, trauma Rapid onset $\pm$ thrombophlebitis, varicosities	Arteriosclerosis, claudication Usually >45 yr Slow progression	Diabetes mellitus Peripheral neuropathy
<b>Common Distribution</b>	Medial malleolus	Distal locations	Pressure point distribution
<b>Appearance</b>	Yellow exudates Granulation tissue	Pale/white, necrotic base $\pm$ dry eschar covering	Necrotic base
<b>Wound Margins</b>	Irregular	Even ("punched out")	Irregular or "punched out" or deep
<b>Depth</b>	Superficial	Deep	Superficial/deep
<b>Surrounding Skin</b>	Venous stasis discolouration (brown)	Thin shiny dry skin, hairless, cool	Thin dry skin $\pm$ hyperkeratotic border Hypersensitive/ischemic
<b>Pulses</b>	Normal distal pulses	Decreased distal pulses	Decreased pulses likely
<b>Vascular Exam</b>	ABI >0.9 Doppler; abnormal venous system	ABI <0.9 Pallor on elevation, rubor on dependency Delayed venous filling	ABI is inaccurately high Usually associated with arterial disease
<b>Pain</b>	Moderately painful Increased with leg dependency, decreased with elevation No rest pain	Extremely painful Decreased with dependency, increased with leg elevation and exercise (claudication) Rest pain	Painless No claudication or rest pain Associated paresthesia, anesthesia
<b>Treatment</b>	Leg elevation, rest Compression at 30 mmHg (stockings or elastic bandages) Moist wound dressings $\pm$ topical, systemic antibiotics $\pm$ skin grafts	Rest, no elevation, no compression Moist wound dressing $\pm$ topical and/or systemic antibiotics Modify risk factors (smoking, diet, exercise, etc.) Vascular surgical consultation Treat underlying conditions (DM, proximal arterial occlusion, etc.)	Control diabetes Careful wound care Foot care Orthotics Early intervention for infections (topical and/or systemic antibiotics) Vascular surgical consultation



ABI in diabetics can be falsely normal due to incompressible arteries secondary to plaques/calcification.



All chronic ulcers require vascular studies and a vascular consult.

## Pressure Ulcers



### Common Sites

- over bony prominences; 95% on lower body

### Stages of Development

1. hyperemia: disappears 1 h after pressure removed
2. ischemia: follows 2-6 h of pressure
3. necrosis: follows >6 h of pressure
4. ulcer: necrotic area breaks down – N.B. skin is like tip of an iceberg

### Classification (National Pressure Ulcer Advisory Panel 2007)

Stage I: nonblanchable erythema present >1 h after pressure relief, skin intact

Stage II: partial-thickness skin loss

Stage III: full-thickness skin loss into subcutaneous tissue, but not through fascia

Stage IV: through fascia into muscle, bone, tendon, or joint

- if an eschar is present, must fully debride before staging possible

### Prevention

- good nursing care (clean dry skin, frequent repositioning), special beds or mattress (Kin Air®), proper nutrition, activity, early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, etc.)

### Treatment

- depends on individual patient and condition
- treat underlying medical issues including nutrition
- continue with preventative measures (pressure relief)
- wound debridement, moisture retentive or antimicrobial dressing, regular reassessment
- topical antimicrobials at treating physician's discretion, systemic antibiotics for infections
- assess for possible reconstruction

### Complications

- cellulitis, osteomyelitis, sepsis, gangrene

## Burns



## Burn Injuries

### Causal Conditions

- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

### Most Common Etiology

- children: scald burns
- adults: flame burns

**Table 15. Skin Function and Burn Injury**

Skin Function	Consequence of Burn Injury	Intervention Required
Thermoregulation	Prone to lose body heat	Must keep patient covered and warm
Control of fluid loss	Loss of large amounts of water and protein from the skin and other body tissues	Adequate fluid resuscitation is imperative
Mechanical barrier to bacterial invasion and immunological organ	High risk of infection	Antibiotic ointments (systemic if signs of specific infection present) Tetanus prophylaxis if necessary



## Pathophysiology of Burn Wounds

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent (see Figure 18)
- **zone of hyperemia:** vasodilation from inflammation; entirely viable, cells recover within 7 d; contributes to systemic consequences seen with major burns
- **zone of stasis (edema):** decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24–48 h without proper treatment
  - factors favoring cell survival: moist, aseptic environment, rich blood supply
  - zone where appropriate early intervention has most profound effect in minimizing injury
- **zone of coagulation (ischemia):** no blood flow to tissue → irreversible cell damage → cellular death/necrosis

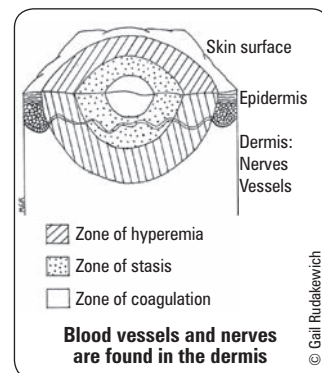


Figure 18. Zones of thermal injury

## Diagnosis and Prognosis

- burn size (see Figure 19)
  - % of TBSA burned: rule of 9s for 2° and 3° burns only (children <10 yr old use Lund-Browder chart – see Figure 20)
  - for patchy burns, surface area covered by patient's palm (fingers closed) represents approximately 1% of TBSA
- age: more complications if <3 or >60 yr old
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see Table 16)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see *Indications for Transfer to Burn Centre*, PL18)
- inhalation injury: can severely compromise respiratory system
- associated injuries (e.g. fractures)
- co-morbid factors (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure) can exacerbate extent of injury

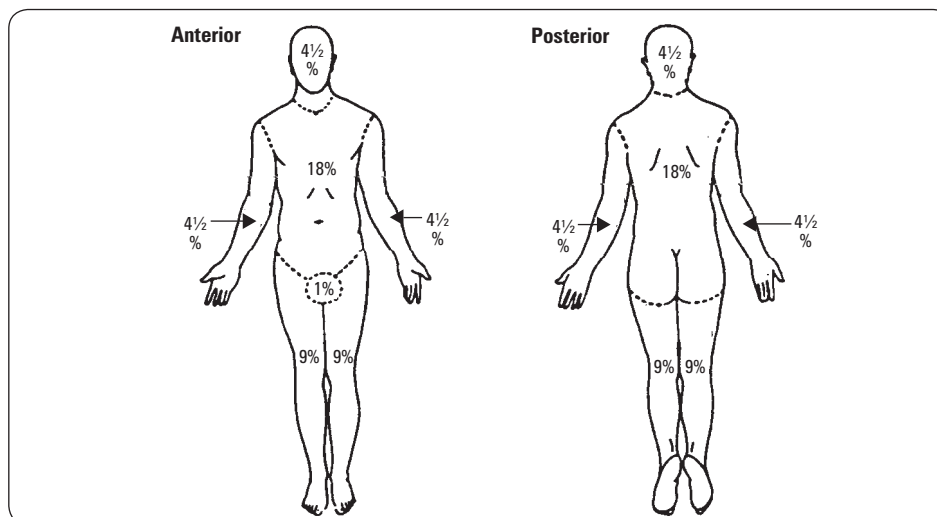


Figure 19. Rule of 9s for TBSA



Prognosis best determined by burn size (TBSA), age of patient, presence/absence of inhalation injury.



Circumferential burns can restrict respiratory excursion and/or blood flow to extremities and require escharotomy.



TBSA does not include areas with 1° burns.

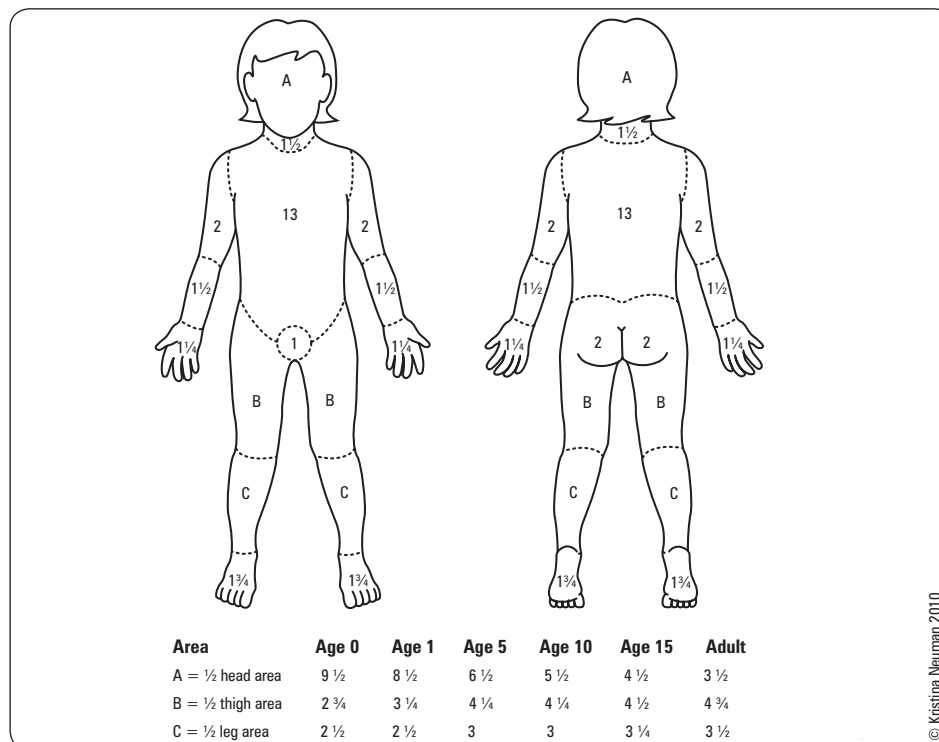


Figure 20. Lund-Browder diagram

Table 16. Burn Depth (1st, 2nd, 3rd degree)

Nomenclature	Traditional Nomenclature	Depth	Clinical Features
Erythema/Superficial	First degree	Epidermis	Painful, sensation intact, erythema, blanchable
Superficial-Partial Thickness	Second degree	Into superficial dermis	Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present
Deep-Partial Thickness	Second degree	Into deep (reticular) dermis	Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn
Full Thickness	Third degree Fourth degree	Through epidermis and dermis Injury to underlying tissue structures (e.g. muscle, bone)	Insensate (nerve endings destroyed), hard leathery eschar that is black, grey, white, or cherry red in colour, hairs do not stay attached, may see thrombosed veins

## Indications for Transfer to Burn Centre

### American Burn Association Criteria

- total 2° and 3° burns >10% TBSA
- burns involving the face, hands, feet, genitalia, perineum, or major joints
- 3° burns in any age group
- electrical burns, including lightning (internal injury underestimated by TBSA)
- chemical burns
- inhalation injury (may lead to respiratory distress)
- burns associated with major trauma/serious illness
- burned children in hospitals without appropriate child burn care
- burns in patients who will require special social, emotional, or rehabilitative intervention.

## Acute Care of Burn Patients

- adhere to ATLS protocol
- resuscitation using Parkland formula to restore plasma volume and cardiac output
  - 4 cc RL/kg/% TBSA over first 24 h (1/2 within first 8 h of sustaining burn, 1/2 in next 16 h)

- extra fluid administration required if
  - burn >80% TBSA
  - 4° burns
  - associated traumatic injury
  - electrical burn
  - inhalation injury
  - delayed start of resuscitation
  - pediatric burns
- monitor resuscitation
  - urine output is best measure: maintain at >0.5 cc/kg/h (adults) and 1.0 cc/kg/h (children <12 yr)
  - maintain a clear sensorium, HR <120/min, MAP >70 mmHg
- burn specific care
  - relieve respiratory distress: intubation and/or escharotomy (see sidebar)
  - prevent and/or treat burn shock: 2 large bore IVs
  - identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
  - determine TBSA affected first, since depth is difficult to determine initially (easier to determine after 24 h)
- tetanus prophylaxis if needed
  - all patients with burns >10% TBSA, or deeper than superficial partial thickness, need 0.5 cc tetanus toxoid
  - also give 250 U of tetanus Ig if prior immunization is absent/unclear, or the last booster >10 yr ago
- baseline laboratory studies (Hb, U/A, BUN, CXR, electrolytes, ECG, cross-match, ABG, carboxyhemoglobin)
- cleanse, debride, and treat the burn injury (antimicrobial dressings)
- early excision and grafting important for outcome

### Respiratory Problems

- 3 major causes
  - burn eschar encircling chest
    - ♦ distress may be apparent immediately
    - ♦ perform escharotomy to relieve constriction
  - CO poisoning
    - ♦ may present immediately or later
    - ♦ treat with 100% O<sub>2</sub> by facemask (decreases half-life of carboxyhemoglobin from 210 to 59 min) until carboxyHb <10%
  - smoke inhalation leading to pulmonary injury
    - ♦ chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
    - ♦ risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
    - ♦ watch for secondary bronchopneumonia (3-25 d) leading to progressive pulmonary insufficiency
    - ♦ intubate patient with any signs of inhalation injuries

### Burn Wound Healing

**Table 17. Burn Shock Resuscitation (Parkland Formula)**

<b>Hour 0-24</b>	4 cc RL/kg/% TBSA with 1/2 of total in first 8 h from time of injury and 1/2 of total in next 16 h from time of injury
<b>Hour 24-30</b>	0.35-0.5 cc plasma/kg/%TBSA
<b>&gt;Hour 30</b>	D5W at rate to maintain normal serum sodium

\*Do not forget to add maintenance fluid to resuscitation

**Table 18. Burn Wound Healing**

Depth	Healing
First degree	No scarring. Complete healing
Second degree (Superficial partial)	Spontaneously re-epithelialize in 7 to 14 d from retained epidermal structures ± residual skin discolouration Hypertrophic scarring uncommon. Grafting rarely required
Deep second degree (Deep partial)	Re-epithelialize in 14-35 d from retained epidermal structures Hypertrophic scarring frequent Grafting recommended to expedite healing
Third degree (Full thickness)	Re-epithelialize from the wound edge Grafting/flap necessary to replace dermal integrity, limit hypertrophic scarring
Fourth degree	Often results in amputations If not requiring amputation, needs flap for coverage after debridement (do not reepithelialize – cannot graft)



#### Signs of CO Poisoning

- Headache
- Confusion
- Coma
- Arrhythmias



#### Inhalation Injuries 101

- Indicators of inhalation injury
  - Injury in a closed space
  - Facial burn
  - Singed nasal hair/eyebrows
  - Soot around nares/oral cavity
  - Hoarseness
  - Conjunctivitis
  - Tachypnea
  - Carbon particles in sputum
  - Elevated blood CO levels (i.e. brighter red)
- Suspected inhalation injury requires immediate intubation due to impending airway edema. Failure to diagnose inhalation injury can result in airway swelling and obstruction, which, if untreated, can lead to death.
- Neither CXR or ABG can be used to rule out inhalation injury.
- Direct bronchoscopy now used for diagnosis.

## Treatment

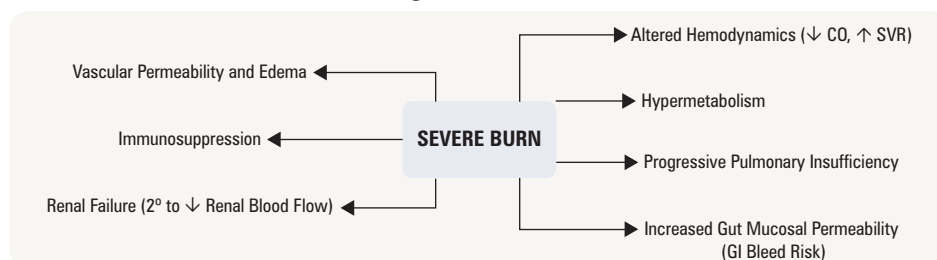
- 3 stages
  - assessment: depth determined
  - management: specific to depth of burn and associated injuries
  - rehabilitation
- first degree
  - treatment aimed at comfort
    - topical creams (pain control, keep skin moist) ± aloe
    - oral NSAIDs (pain control)
- superficial second degree
  - daily dressing changes with topical antibiotics, polysporin, may use a temporary biological or synthetic covering to close the wound; leave blisters intact unless circulation impaired or unless over joint inhibiting motion
- deep second degree and third degree
  - prevent infection and sepsis (significant cause of death in burn patients)
    - most common organisms: *S. aureus*, *P. aeruginosa* and *C. albicans*
      - day 1-3 (rare): Gram-positive
      - day 3-5: Gram-negative (*Proteus*, *Klebsiella*)
    - topical antimicrobials: prevent bacterial infection (from skin flora, gut flora or caregiver) and secondary sepsis (see Table 19)
  - remove dead tissue
    - surgically debride necrotic tissue, excise to viable (bleeding) tissue

**Table 19. Topical Antibiotic Therapy for Burns**

Antibiotic	Pain with Application	Penetration	Adverse Effects
Silver nitrate (0.5% solution)	None	Minimal	May cause methemoglobinemia, stains (black), leaches sodium from wounds
Nanocrystalline silver-coated dressing (Acticoat®)	None or transient	Medium, does not penetrate eschar. Preferred over silver sulfadiazine and silver nitrate	May stain, producing a pseudoeschar or facial discolouration (argyria-like symptoms); raised liver enzymes
Silver sulfadiazine (cream) (Silvadene®)	Minimal	Medium, does not penetrate eschar	Slowed healing, leukopenia, mild inhibition of epithelialization
Mafenide acetate (solution/cream) (Sulfamylon®)	Moderate	Well, penetrates eschar	Mild inhibition of epithelialization, may cause metabolic acidosis with wide application

- early excision and grafting is the mainstay of treatment
- initial dressing should decrease bacterial proliferation
- indication for skin graft: deep 2° or 3° burn that is > size of a quarter
- prevention of wound contractures: pressure dressings, joint splints, early physiotherapy

## Other Considerations in Burn Management



**Figure 21. Systemic effects of severe burns**

- nutrition
  - hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
  - calories, vitamin C, vitamin A,  $\text{Ca}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Fe}^{2+}$
- immunosuppression and sepsis
  - must keep bacterial count <10<sup>5</sup> bacteria/g of tissue (blood culture may not be positive)
  - signs of sepsis: sudden onset of hyper/hypothermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 h post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
- GI bleed may occur with burns >40% TBSA (usually subclinical)
  - treatment: tube feeding or NPO, antacids, H<sub>2</sub> blockers (preventative)
- renal failure secondary to under resuscitation, drugs, myoglobin, etc.
- progressive pulmonary insufficiency
  - can occur after: smoke inhalation, pneumonia, cardiac decompensation, sepsis
- wound contracture and hypertrophic scarring
  - largely preventable with timely wound closure, splinting, pressure garments and physiotherapy



### Risk Factors for Infection of Burn Wounds

#### Patient Related

- Extent > 30% TBSA
- Depth: full-thickness and deep partial-thickness
- Patient age (higher risk with very young and very old)
- Co-morbidities
- Wound dryness
- Wound temperature
- Secondary impairment of blood flow to wound
- Acidosis

#### Microbial Factors

- Density > 10<sup>5</sup> organisms per gram tissue
- Motility
- Virulence and metabolic products (endotoxin, exotoxin, permeability factors, other factors)
- Antimicrobial resistance



### Meta-Analysis of Early Excision of Burns

Burns 2006;32:145-150

**Purpose:** To determine if early excision and grafting is superior (or equivalent) to conservative treatment and delayed grafting once the burn eschar has separated.

**Methods:** A literature review was completed seeking prospective randomized controlled trials comparing early excision (<7 d) and immediate grafting against treatment with dressings followed by grafting post-eschar separation. All ages and burn severities were included. Outcomes were mortality, blood transfusions, wound healing time and length of hospital stay.

**Results:** A total of 361 patients from 7 randomized controlled trials were included in the meta-analysis. 180 patients received early intervention and 181 received conservative management. There was no significant difference in mortality in patients with inhalational injury. Early excision and grafting in patients without inhalational injury resulted in significantly reduced mortality (RR 0.36,  $p < 0.05$ ) and decreased length of hospitalization by 8.89 d ( $p < 0.05$ ). The number of patients requiring blood transfusion was significantly higher with early excisional management (SMD 1.65,  $p < 0.05$ ). There was no significant difference in wound healing time between the two groups.

**Conclusion:** Early excision of burns (<7 d) is beneficial in reducing mortality in patients without inhalational injury, along with reducing length of time spent in hospital.

## Special Considerations

### CHEMICAL BURNS

- major categories: acid burns, alkaline burns, phosphorous burns, chemical injection injuries
- common agents: cement, hydrofluoric acid, phenol, tar
- mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
  - acids → coagulation necrosis
  - alkalines → saponification followed by liquefactive necrosis
- severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
- burns are deeper than they initially appear and may progress with time

### Treatment (general)

- ABCs, monitoring
- remove contaminated clothing and brush off any dry powders before irrigation
- irrigation with water for 1-2 h under low pressure (contraindicated in heavy metal burns, such as sodium, potassium, magnesium, and lithium; in these cases soak in mineral oil instead)
- inspect eyes, if affected: wash with saline and refer to ophthalmology
- inspect nails, hair and webspaces
- correct metabolic abnormalities and tetanus prophylaxis if necessary
- local wound care 12 h after initial dilution (debridement)
- wound closure same as for thermal burn
- beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

### ELECTRICAL BURNS

- depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
- often presents as small punctate burns on skin with extensive deep tissue damage which requires debridement
- electrical burns require ongoing monitoring as latent injuries can occur
- watch for system specific damages and abnormalities:
  - abdominal: intraperitoneal damage
  - bone: fractures and dislocations especially of the spine and shoulder
  - cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
  - muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
  - neurological: seizures and spinal cord damage
  - ophthalmology: cataract formation (late complication)
  - renal: ATN resulting from toxic levels of myoglobin and hemoglobin
  - vascular: vessel thrombosis → tissue necrosis (increased Cr, K<sup>+</sup> and acidity), decrease in RBC (beware of hemorrhages/delayed vessel rupture)

### Treatment

- ABCs, primary and secondary survey, treat associated injuries
- monitor: hemochromogenuria, compartment syndrome, urine output
- wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
- debride non-viable tissue early and repeat prn (every 48 h) to prevent sepsis
- amputations frequently required

### FROSTBITE

- see [Emergency Medicine](#), ER45



Speed is essential in the management of chemical burns as chemicals can continue to cause damage until they are removed or neutralized.



**Tar:** remove with repeated application of petroleum-based antibiotic ointments (e.g. Polysporin®).



#### Treatment (specific)

**Acid burns:** water irrigation followed by dilute solution of sodium bicarbonate  
**Hydrofluoric acid:** water irrigation; clip fingernails to avoid acid trapping; topical calcium gel ± subcutaneous injection of calcium gluconate ± 10% calcium gluconate IV depending on amount of exposure and pain  
**Sulfuric acid:** treat with soap/lime prior to irrigation, as direct water exposure produces extreme heat



#### Tissue Resistance to Electrical Current:

nerve < vessel/blood < muscle < skin  
 < tendon < fat < bone



# Hand



High pressure injection injury is deceptively benign-looking (small pinpoint hole on finger pad) often with few clinical signs. Intense pain and tenderness, along the course the foreign material traveled, is present a few hours after the injury. Definitive treatment is exposure and removal of foreign material.

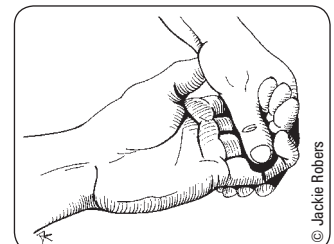


**Allen's Test:** while patient's hand is firmly closed, occlude both radial and ulnar arteries. Once fist is open, release either artery and assess collateral flow.

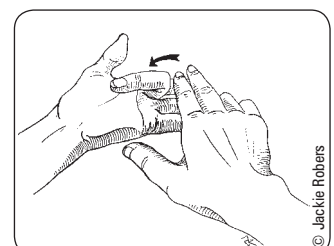


## Approach to Hand Lacerations

**TIN AX**  
Tetanus prophylaxis  
Irrigate with NS  
**NPO**  
Antibiotic prophylaxis  
X-rays



**Figure 22. Testing profundus (FDP) – inserts at distal phalanx**



**Figure 23. Testing superficialis (FDS) – inserts at middle phalanx**



Never blindly clamp a bleeding vessel as nerves are often found in close association with vessels.



Never explore any volar hand wound in the ER!

## Traumatic Hand

**Table 20. Key Features of the History and Physical Exam of the Injured Hand in the Emergency Department**

HISTORY		
<b>Key Questions</b>	Age Hand dominance Occupation Time and place of accident Mechanism of injury Tetanus status	
PHYSICAL EXAM	Structure	Examination
<b>Observation</b>	Position of finger Deformity Bruising or swelling Sweating pattern Anatomical structures beneath	Abnormal cadence (fingers normally slightly flexed), scissoring Bony or specific (e.g. mallet, swan neck) May indicate underlying skeletal injury May indicate denervation If open laceration, need to explore within wound (under sterile conditions)
<b>Vascular Status</b>	Radial and ulnar arteries Digital arteries Temperature and skin turgor	Allen's Test (see sidebar) Capillary refill (<2-3 s) For each test, need to compare both sides
<b>Sensory (refer to Figure 3)</b>	Median nerve Ulnar nerve Radial nerve Digital nerves	Dorsal radial tip of index finger Dorsal ulnar tip of little finger Dorsal web space of the thumb 2 point discrimination of each finger
<b>Motor Function</b>	Median nerve Ulnar nerve Radial nerve	Extrinsic muscles: flex DIP of index finger ("OK sign") Intrinsic muscles: thumb to ceiling with palm up Extrinsic muscles: flex DIP of little finger Intrinsic muscles: abduct index finger ("Peace sign") or patient able to hold piece of paper between adducted fingers and resist pulling Extrinsic muscles: extend thumb ("thumb's up") and wrist
<b>Range of Motion</b>	Tendons, bones, joints, nerves	Assess active and passive range of motion of wrist extension/flexion/ulnar/radial deviation, finger abduction/adduction/flexion/extension, thumb flexion/extension/abduction/adduction/circumflexion
<b>Tendons</b>	Flexor digitorum profundus (FDP) Flexor digitorum superficialis (FDS)	Stabilize PIP joint in extension, ask patient to flex fingers (at DIP) (see Figure 22) Stabilize non-exam fingers in extension (neutralizes FDP) and ask patient to flex examination finger (see Figure 23)
<b>Palpation</b>	Bones Joints	Focal tenderness or abnormal alignment Instability may indicate ligamentous injury or dislocation

## General Management

### Nerves

- direct repair for a clean injury within 14 d and without concurrent major injuries → otherwise secondary repair
- epineurial repair of digital nerves with minimal tension
- post-operative: dress wound, elevate hand and immobilize
- Tinel's sign (cutaneous percussion over the repaired nerve) produces paresthesias and defines level of nerve regeneration
  - Wallerian degeneration occurs in the first 2 wk, which is why there is no Tinel's sign till after this time period
  - a peripheral nerve regenerates at 1 mm/d
  - paresthesias felt at area of percussion because re-growth of myelin (Schwann cells) is slower than axonal re-growth → percussion on exposed free-end of axon generates paresthesia



### Vessels

- often associated with nerve injury (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 h
- dress, immobilize, and splint hand with finger tips visible
- monitor colour, capillary refill, skin turgor, fingertip temperature post-revascularization

### Tendons

- most tendon lacerations require primary repair
- many extensors are repaired in the emergency room, flexors are repaired in the operating room within 2 wk
- avoid excessive immobilization (specific protocols for flexors, 2-3 wk for extensors) to minimize stiffness and facilitate rehabilitation

### Bones

- see *Fractures and Dislocations*, PL25

### Nailbed

- remove nail to examine underlying nailbed under digital block anesthesia
- irrigate wound and nail thoroughly
- suture repair of nailbed with catgut suture
- replace cleaned nail, which acts as splint for any underlying distal phalangeal fracture and prevents adhesion formation between nail fold and nailbed



Arterial bleeding from a volar digital laceration may indicate nerve laceration (nerves in digits are superficial to arteries).



#### Compartment Syndrome

Watch out for these signs with a closed or open injury: tense, painful extremity (worse on passive stretch), paresthesia/paralysis, pallor, distal pulselessness (often late in process), and contracture (irreversible ischemia). Intracompartmental pressures can be measured (normal pressure = up to 12 mmHg), but a clinical diagnosis is an indication for an emergent fasciotomy. If untreated, end result is ischemic contracture of the extremity (Volkmann's contracture).

## Hand Infections

### Principles

- trauma is most common cause
- 5 cardinal signs: *rubor* (red), *calor* (hot), *tumour* (swollen), *dolor* (painful) and *functio laesa* (loss of function)
- 90% caused by Gram-positive organisms
- most common organisms (in order) – *S. aureus*, *S. viridans*, Group A *Streptococcus*, *S. epidermidis*, and *Bacteroides melaninogenicus* (MRSA becoming more common)

### TYPES OF INFECTIONS

#### Deep Palmar Space Infections

- uncommon, involve thenar or mid-palm, treated in OR

#### Felon

- **definition:** subcutaneous abscess in the fingertip that commonly occurs following severe paronychia or a puncture wound into the pad of digit; may be associated with osteomyelitis
- **treatment:** elevation, warm soaks, cloxacillin 500 mg PO q6h (if in early stage); if obvious abscess then I&D and PO cloxacillin

#### Flexor Tendon Sheath Infection

- *Staphylococcus* > *Streptococcus* > Gram-negative rods
- **definition:** acute suppurative tenosynovitis commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated
- **clinical features:** Kanavel's 4 cardinal signs:
  1. point tenderness along flexor tendon sheath (earliest and the most important)
  2. severe pain on passive extension of DIP (second most important)
  3. fusiform swelling of entire digit
  4. flexed posture (increased comfort)
- **treatment**
  - OR incision and drainage, irrigation, IV antibiotics, and resting hand splint until infection resolves

#### Herpetic Whitlow

- HSV-1, HSV-2
- **definition:** painful vesicle(s) around fingertip
  - often found in medical/dental personnel and children
- **clinical features:** can be associated with fever, malaise and lymphadenopathy
  - patient is infectious until lesion has completely healed
- **treatment:** routine culture and viral prep protection (cover), consider oral acyclovir; do not break blisters, as this can spread infection

#### Paronychia

- acute = *Staphylococcus*; chronic = *Candida*
- **definition:** infection (granulation tissue) of soft tissue around fingernail (beneath eponychial fold)

- **etiology**
  - acute paronychia: a “hangnail”, artificial nails, and nail biting
  - chronic paronychia: prolonged exposure to moisture
- **treatment**
  - acute paronychia: warm compresses and cephalexin 500 mg PO q6h ± drainage if abscess present
  - chronic paronychia: anti-fungals with possible debridement and marsupialization, removal of nail plate

## Amputations

### Hand or Finger

- emergency management: injured patient and amputated part require attention
  - **patient:** x-rays, NPO, clean wound and irrigate with NS, dress stump with nonadherent, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/erythromycin)
  - **amputated part:** x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice
- **indications for replantation**
  - **age:** children often better results than adults
  - **level of injury:** proximal, thumb and multiple digit amputations are higher priority
  - **nature of injury:** clean cut injuries have higher successful replantation rate; avulsion and crush injuries are relative contraindications to replant
- if replant contraindicated manage stump with revision amputation
  - would only allow a fingertip injury to heal by secondary intention

## Tendons

### Common Extensor Tendon Deformities

Table 21. Extensor Tendon Deformities

Injury	Definition	Zone	Etiology/Clinical Features	Treatment
<b>Mallet Finger</b>	DIP flexed with loss of active extension (see Figure 25)	1	Forced flexion of the extended DIP joint leading to extensor tendon rupture at DIP joint (e.g. sudden blow to tip of the finger)	Splint DIP in extension for 6 wk followed by 2 wk of night splinting. If inadequate improvement after 6 wk, check splinting routine and recommend 4 more wk of continuous splinting
<b>Boutonniere Deformity</b>	PIP flexed, DIP hyperextended (see Figure 26)	3	Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx Associated with RA or trauma (laceration, volar dislocation, acute forceful flexion of PIP)	Splint PIP in extension and allow active DIP motion
<b>Swan Neck Deformity</b>	PIP hyperextended, DIP flexed (see Figure 27)	3	Trauma (PIP volar plate injury) Associated with RA and old, untreated mallet deformity	Splint to prevent PIP hyperextension or DIP flexion Consider arthrodesis/arthroplasty

### De Quervain's Tenosynovitis (zone 7; most common cause of radial wrist pain)

- **definition:** inflammation in 1st extensor compartment (APL and EPB)
- **clinical features:**
  - +ve Finkelstein's test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)
  - pain localized to the 1st extensor compartment
  - tenderness and crepitation over radial styloid may be present
  - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)
- **treatment:**
  - mild: NSAIDs, splinting and steroid injection into the tendon sheath (successful in over 60% of cases)
  - severe: surgical release of stenotic tendon sheaths (APL and EPB); remember there may be 2 or more sheaths

### Ganglion Cyst (zone 7)

- **definition:**
  - fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin
  - most common soft tissue tumour of hand and wrist (60% of masses)

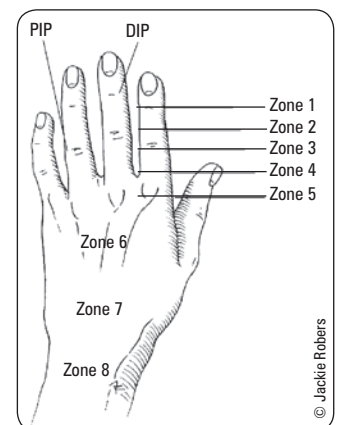


Figure 24. Zone of extensor tendon injury (odd numbered zones fall over a joint)

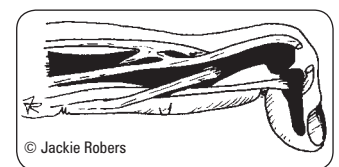


Figure 25. Mallet finger deformity

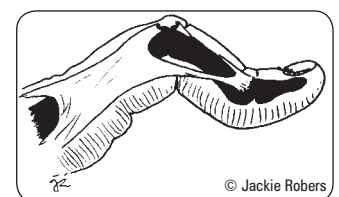


Figure 26. Boutonniere deformity

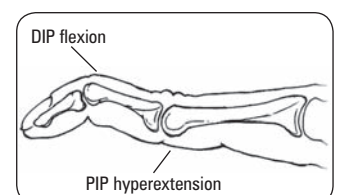


Figure 27. Swan neck deformity

- **clinical features:**
  - most common around scapholunate ligament junction
  - 3 times more common in women than in men
  - more common in younger individuals
  - can be large or small – may drain internally so size may wax and wane
  - often non-tender although tenderness increased when cyst smaller (from increased pressure within smaller cyst sac)
- **treatment:**
  - conservative treatment: watch and wait
  - aspiration (recurrence rate 65%)
  - consider operative excision of cyst and stalk (recurrence is possible)
  - steroids if painful

### Common Flexor Tendon Deformities (see Figure 28)

- flexor tendon zones (important for prognosis of tendon lacerations)
- “no-man’s land”:
  - between distal palmar crease and mid-middle phalanx
  - zone where superficialis and profundus lie ensheathed together
  - recovery of glide very difficult after injury

### Stenosing Tenosynovitis (trigger finger/thumb)

- **definition:** inflammation of synovium causes size discrepancy between tendon and sheath/pulley (most commonly at A-1 pulley) = locking of thumb or finger in flexion/extension
- **etiology:** idiopathic or associated with RA, diabetes, hypothyroidism and gout
- **clinical features:**
  - thumb, ring and long fingers most commonly affected
  - patient complains of catching, snapping or locking of affected finger
  - tenderness to palpation/nodule at palmar aspect of MCP over A-1 pulley
  - women are 4 times more likely than men to be affected
- **conservative treatment:**
  - NSAIDs
  - steroid injection
  - surgical flexor tendon release
  - injections less likely to be successful in patients with DM or symptoms greater than 6 mo
- **surgical treatment:**
  - incise A-1 flexor tendon pulley to permit unrestricted, full active finger motion



A-2 and A-4 pulleys are most important for function; prevent bowstringing of tendons.

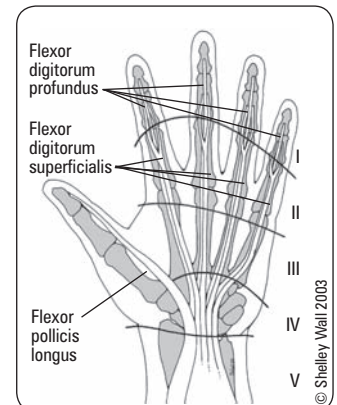


Figure 28. Zones of the flexor tendons

## Fractures and Dislocations

- for fracture principles, see [Orthopedics](#), OR5

### FRACTURES

- about 90% of hand fractures are stable in flexion (lock/prevent extension)
- **position of function** (like a hand holding a pop can) (see Figure 29):
  - wrist extension 15°
  - MCP flexion 45°
  - IP flexion (slight)
  - thumb abduction/rotation
  - contraindications: post repair of flexor tendons, median/ulnar nerve injury
- **position of safety** (see Figure 30):
  - wrist extension 45° (position most beneficial for hand function if immobilized)
  - MCP flexion 60° (maximal collateral ligament stretch)
  - PIP and DIP in full extension (maximal volar plate origin stretch)
  - thumb abduction and opposition (functional position)
- stiffness secondary to immobilization is the most important complication; Tx = early motion

### Distal Phalanx Fractures

- most commonly fractured bone in the hand
- usual mechanism is crush injury and thus accompanied by soft tissue injury
- subungual hematoma is common and must be decompressed if painful or nail removed
- treatment consists of 3 wk of digital splinting (with IP joint movement preserved)

### Proximal and Middle Phalanx Fractures

- check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit
- undisplaced or minimally displaced: closed reduction (if extra-articular) buddy tape to neighbouring stable digit, elevate hand, motion in guarded fashion 10-14 d post injury
- displaced, non-reducible, not stable with closed reduction, or rotational or scissoring deformity: percutaneous pins (K-wires) or ORIF, and splint

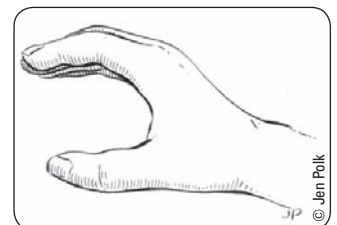


Figure 29. Position of function

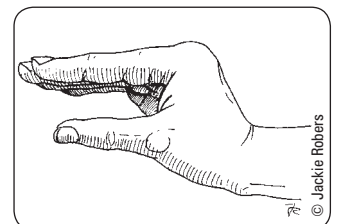


Figure 30. Position of safety

### Metacarpal Fractures

- generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
- Boxer's fracture (extra-articular):** acute angulation of neck of metacarpal of little finger into palm (see Figure 31)
  - mechanism: blow on the distal-dorsal aspect of closed fist
  - loss of prominence of metacarpal head, volar displacement of head
  - check for scissoring of fingers on making a fist
  - up to 30-40° angulation may be acceptable
  - closed reduction should be considered to decrease the angle
  - if stable ulnar gutter splint x 3 wk with PIP and DIP joints free
- Bennett's fracture (intra-articular):** fracture/dislocation of the base of the thumb metacarpal (see Figure 32)
  - unstable fracture
  - abductor pollicis longus pulls MC shaft proximally and radially causing adduction of thumb
  - treat with percutaneous pinning, thumb spica x 6 wk
- Rolando's fracture (intra-articular):** T- or Y-shaped fracture of the base of the thumb metacarpal (see Figure 33)
  - treat with ORIF with K-wire

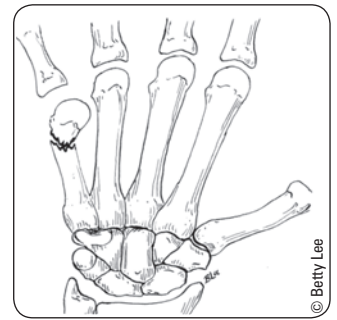


Figure 31. Boxer's fracture

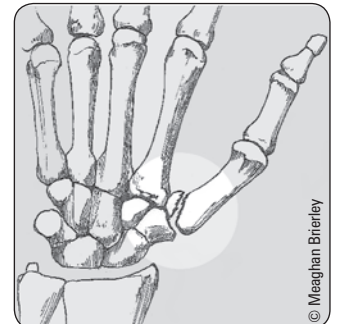


Figure 32. Bennett's fracture

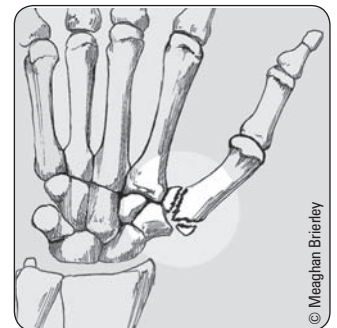


Figure 33. Rolando's fracture

### DISLOCATIONS

- must be reduced as soon as possible

#### PIP and DIP Dislocations (PIP more common than DIP)

- usually dorsal dislocation (commonly from hyperextension)
- if closed dislocation: closed reduction and splinting (30° flexion for PIP and full extension for DIP) or buddy taping and early mobilization (prolonged immobilization causes stiffness)
- open injuries are treated with wound care, closed or open reduction and antibiotics

#### MCP Dislocations (relatively rare)

- dorsal dislocations much more common than volar dislocations
- dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
- two types of dorsal dislocation:
  - simple (reducible with manipulation): treat with 2 wk of splinting at 30° MCP flexion
  - complex (volar plate blocks reduction): treat with open reduction and A1 pulley release + extension-blocking splint at 30° flexion (2 wk) then 10° flexion (2 wk)

#### Ulnar Collateral Ligament (UCL) Injury

- forced abduction of thumb (e.g. ski pole injury)
- skier's thumb:** acute UCL injury
- gamekeepers thumb:** chronic UCL injury
- evaluation:** radially deviate joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion
- Stener's lesion:** the UCL has bony attachments to the adductor aponeurosis and the proximal ligament can displace while the distal attachment remains deep to the aponeurosis, forming a barrier that blocks healing and leads to chronic instability; requires surgery

## Dupuytren's Disease

### Definition

- contraction of longitudinal palmar fascia, forming nodules (usually painless), fibrous cords and eventually flexion contractures at the MCP and interphalangeal joints (see Figure 34)
- flexor tendons not involved
- Dupuytren's diathesis: early age of onset, strong family history, and involvement of sites other than palmar aspect of hand

### Epidemiology

- genetic disorder, unusual in patients from African and Asian countries, high incidence in northern Europeans, men > women, often presents in 5th-7th decade of life, associated with but not caused by alcohol use and diabetes

### Clinical Features

- order of digit involvement (most common to least common): ring > little > long > thumb > index
- may also involve feet (Lederhosen's) and penis (Peyronie's – see [Urology](#), U29)

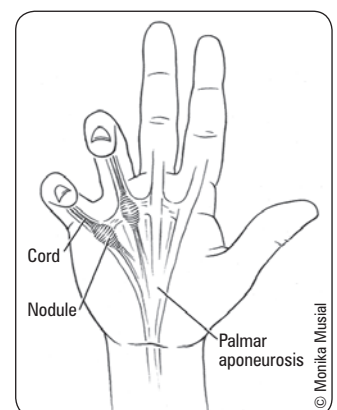


Figure 34. Dupuytren's disease

## Treatment

- stages:
  1. palmar pit or nodule: no surgery
  2. palpable band/cord with no limitation of extension of either MCP or PIP: no surgery
  3. lack of extension at MCP or PIP: surgical fasciectomy indicated
  4. irreversible periarticular joint changes/scarring: surgical treatment possible but poorer prognosis compared to stage 3
- indications for percutaneous release:
  - functional impairment
  - MCP joint contractures  $>30^\circ$
  - any PIP contracture
  - rapidly progressive disease
- may recur, especially in Dupuytren's diathesis

## Carpal Tunnel Syndrome

### Definition

- median nerve compression at the level of the flexor retinaculum as opposed to pronator teres syndrome

### Etiology

- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumours, hypertrophic synovial tissue, fracture callus, and osteophytes), metabolic and physiological (pregnancy, hypothyroidism, acromegaly, and RA), infections, neuropathies (associated with DM or alcoholism), and familial disorders
- job/hobby related repetitive trauma, especially forced wrist flexion

### Epidemiology

- female:male = 4:1, **most common entrapment neuropathy**

### Clinical Features

- sensory loss in median nerve distribution i.e. radial 3.5 digits (see Figure 3)
- discriminative touch often lost first
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/rubbing
- decreased light touch and 2-point discrimination, especially fingertips
- advanced cases: thenar wasting/weakness
- $\pm$  Tinel's sign (tingling sensation on percussion of nerve)
- $\pm$  Phalen's sign (wrist flexion induces symptoms)

### Investigations

- clinical diagnosis
- NCV and EMG may confirm, but do not exclude, the diagnosis

### Treatment

- avoid repetitive wrist and hand motion, wrist splints when repetitive wrist motion required
- conservative: night time splinting to keep wrist in neutral position
- medical: NSAIDs, local corticosteroids injection, oral corticosteroids
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: numbness and tingling  $\pm$  sensory loss, weakness  $\pm$  muscle atrophy, unresponsive to conservative measures
- complications of surgery: injury to median motor branch, palmar cutaneous branch or superficial transverse vascular arch, local pain (pillar pain), and scar formation



#### Accuracy of the Clinical Assessment for Carpal Tunnel Syndrome

- Phalen's:
  - Sensitivity: 0.75 Specificity: 0.47
- Tinel's:
  - Sensitivity: 0.60 Specificity: 0.67
- Carpal Tunnel Compression Test:
  - Sensitivity: 0.87 Specificity: 0.90

Hand Surgery Update 1996; p.223



#### Development and Validation of Diagnostic Criteria for Carpal Tunnel Syndrome

J Hand Surg 2006;31:919-924

**Purpose:** To develop a clinical diagnostic criteria for carpal tunnel syndrome that modeled the clinical diagnostic practices of experts.

**Methods:** Out of 57 clinical findings associated with CTS, eight were ranked highly by a panel of expert clinicians. Using 256 case histories, a panel of experts decided whether a case did or did not have a diagnosis of CTS. This diagnosis represented the dependent variable for a logistic regression model, to which the eight clinical findings were applied. The regression model was then validated against the consensus of a second panel on the diagnosis of CTS for the case histories.

**Results/Conclusions:** The correlation between the probability of CTS predicted by the regression model and the panel of clinicians was 0.71. Clinical diagnostic criteria that contributed significantly to the model were

1. Numbness and tingling in median nerve distribution
2. Nocturnal numbness
3. Weakness and/or atrophy of the thenar musculature
4. Tinel's sign
5. Phalen's test
6. Loss of 2-point discrimination



#### Radiographic Evolution of the Rheumatoid Hand

**Earliest sign:** erosion of the ulnar styloid.

**Progression:** characterized by symmetrical joint space narrowing and erosions of the carpal bones, MCP and PIP (with DIP relatively spared).

**Late stage:** Swan neck and Boutonniere deformities.

## Rheumatoid Hand

### General Principles

- non-surgical treatments form the foundation in the management of the rheumatoid hand
- surgery only for patients whose goals (improved cosmesis or function) may be achieved

### Surgical Treatment of Common Problems

- synovitis: requires tendon repair if ruptured; can lead to carpal tunnel syndrome and trigger finger
- ulnar drift: MCP arthroplasty, resection of distal ulna, soft tissue reconstruction around wrist
- thumb deformities: can be successfully treated by arthrodesis (surgical fixation of joint to promote bone fusion)



## Brachial Plexus

### Etiology

- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumours, ectopic ribs

### Common Palsies

**Table 22. Named Neonatal Palsies of the Brachial Plexus**

Palsy	Location of Injury	Mechanism of Injury	Features
<b>Duchenne-Erb Palsy</b>	Upper brachial plexus (C5-C6)	Head/shoulder distraction (e.g. motorcycle)	Waiter's tip deformity (shoulder internal rotation, elbow extension, wrist flexion)
<b>Klumpke's Palsy</b>	Lower brachial plexus (C7-T1)	Traction on abducted arm	May include Horner's syndrome ("claw hand")

### Differential Diagnosis

- trauma (blunt, penetrating)
- thoracic outlet syndrome
  - neurogenic: associated with cervical rib; compression of C8/T1
  - vascular: pain or sensory symptoms without cervical rib; cessation of radial pulse with provocative maneuvers
- tumour
  - schwannoma: well-defined margins makes it easier for total resection
  - neurofibromas: associated with neurofibromatosis type I
  - other: e.g. Pancoast syndrome (apical lung tumour)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

### Investigations

- EMG
- MRI: gold standard for identifying soft tissue masses
- CT myelogram: better than MRI for identification of nerve root avulsion and identification of pseudomeningocele. Important for preoperative identification of patients likely to require neurotisation procedures (especially for patients with blunt trauma)

### Management

**Table 23. Management of Brachial Plexus Injuries**

	Type	Treatment
<b>Non-Penetrating Trauma</b>	Concussive/compressive	Usually improves (unless expanding mass, e.g. hematoma)
	Traction/stretch	If no continued insult, follow for 3-4 mo for improvement
	Obstetric palsy	Surgery if no significant improvement and/or residual paresis at 6 mo of age
<b>Penetrating Trauma</b>	Sharp or vascular injury	Explore immediately in OR

## Craniofacial Injuries



- low velocity vs. high velocity injuries determine degree of damage
- fractures cause bruising, swelling and tenderness → loss of function
- frequency: nasal > zygomatic > mandibular > maxillary
- management: can wait 5-10 d for swelling to decrease before ORIF required



## Approach to Facial Injuries

- ATLS protocol
- inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve)
- visual assessment
- tetanus prophylaxis
- radiological evaluation
- wound irrigation with NS/RL and remove foreign materials
- conservative debridement of detached or nonviable tissue
- repair when patient's general condition allows (soft tissue injury: <8 h preferable)

### Investigations (see Table 24)

- CT:
  - axial and coronal (specifically request 1.5 mm cuts): for fractures of upper and middle face (not good for mandible)
  - indicated for high velocity trauma, complex facial fractures, orbital floor, panface fractures, pre-op assessment
- panorex radiograph: shows entire upper and lower jaw; best for isolated mandible fracture as patient must be able to sit

**Table 24. Imaging of the Craniofacial Skeleton**

Structure	Appropriate Imaging
<b>Mandible</b>	Panoramic (panorex)* CT
<b>Zygomatic and orbital bones</b>	CT scan* Water's view (occipitomeatal, A-P "from below"), Town's, AP
<b>Nasal bones</b>	No x-ray required – clinical
<b>Maxilla</b>	CT scan – axial and coronal*

\*Best imaging method

### Treatment

- consultation when indicated (dentistry, ophthalmology)
- re-establish normal occlusion
- pursue normal eye function
- restore stability of face and appearance

### Complications

- diplopia/enophthalmos/blindness
- intracranial pathology such as CSF leak, bleeding and SIADH
- sinusitis
- functional abnormalities (i.e. malocclusion)
- infection – extremely rare
- poor cosmesis; need for 2° surgery



Patients with major facial injuries are at risk of developing upper airway obstruction (displaced blood clots, teeth or fracture fragments; swelling of pharynx and larynx; loss of support of hyomandibular complex → retroposition of tongue). Also at risk of ocular injury.



Suspect C-spine injury with any facial trauma. C-spine evaluation before radiographs are ordered.



Consider intracranial trauma; rule out skull fracture.



#### Signs of Basal Skull Fracture

- Battle's sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF otorrhea



Facial bone injuries with orbit involved require ophthalmology consult.

## Mandibular Fractures

- always two points of injury since it is a ring structure (includes fractures and dislocations)
- commonly at sites of weakness (condylar neck, angle of mandible, region of 3rd molar or canine tooth)

### Etiology

- anterior force: bilateral fractures
- lateral force: ipsilateral subcondylar and contralateral angle or body fracture
- note: classified as open if fracture into tooth bearing area (alveolus)

### Clinical Features

- pain, swelling, difficulty opening mouth ("trismus")
- malocclusion, asymmetry of dental arch
- damaged, loose, or lost teeth
- palpable "step" along mandible
- numbness in V3 distribution
- intra-oral lacerations or hematoma (sublingual)
- chin deviating toward side of a fractured condyle

## Classification

**Table 25. Mandibular Fracture Classifications by Anatomic Region (refer to Figure 35)**

	Areas/Boundaries
<b>Symphysis</b>	Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible
<b>Body*</b>	From the symphysis to the distal alveolar border of the third molar
<b>Angle</b>	Triangular region between the anterior border of the masseter and the posterosuperior insertion of the masseter distal to the third molar
<b>Ramus</b>	Part of the mandible that extends posteriosuperiorly into the condylar and coronoid processes
<b>Condylar</b>	Area of condylar process of mandible
<b>Subcondylar</b>	Area below the condylar neck (i.e. sigmoid notch) of the mandible
<b>Coronoid Process</b>	Area of the coronoid process of mandible

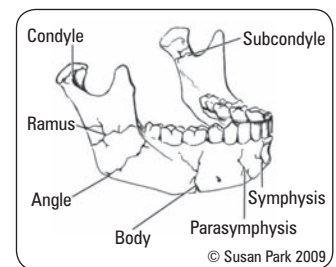
\*Most common mandibular fracture type

## Treatment

- maxillary and mandibular arch bars wired together (intramaxillary fixation) or ORIF
- antibiotics to cover against *S. aureus* and anaerobes

## Complications

- malocclusion, malunion
- tooth loss, and possible sensation loss
- TMJ ankylosis



**Figure 35. Mandibular fracture**

## Maxillary Fractures

**Table 26. Le Fort Classification (refer to Figure 36)**

	Le Fort I	Le Fort II	Le Fort III
<b>Alternative Name</b>	Guerin fracture	Pyramidal fracture	Craniofacial dysjunction
<b>Type of Fracture</b>	Horizontal	Pyramidal	Transverse
<b>Structures Involved</b>	Piriform aperture Maxillary sinus Pterygoid plates	Nasal bones Medial orbital wall Maxilla Pterygoid plates	Nasofrontal suture Zygomaticofrontal suture Zygomatic arch Pterygoid plates
<b>Anatomical Result</b>	Maxilla divided into 2 segments	Maxillary teeth separated from face	Detach entire midfacial skeleton from cranial base

## Nasal Fractures

### Etiology

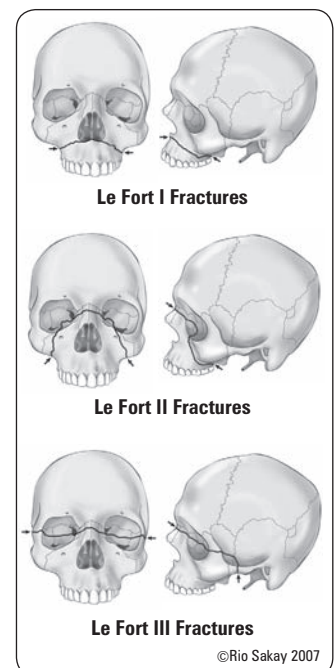
- lateral force → more common, good prognosis
- anterior force → can produce more serious injuries
- most common facial fracture

### Clinical Features

- epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum, crepitus, septal hematoma, respiratory obstruction, subconjunctival hemorrhage
- depression and splaying of nasal bones causing a saddle deformity
- important to clinically assess for naso-orbital ethmoid (NOE) fractures

### Treatment

- in the absence of complications, no treatment required
- closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with Adaptic®, nasal splint for 7 d
- best reduction immediately (<6 h) or when swelling subsides (5-7 d)
- rhinoplasty may be necessary later for residual deformity (30%)



**Figure 36. Le Fort fractures**



Always drain septal hematomas as this is a cause of septal necrosis with perforation (saddle nose deformity).

## Naso-orbital Ethmoid Fractures

### Etiology

- fractures of the nasal and ethmoid bones of the medial orbit
- problematic and may lead to greatest change in facial appearance
- Markowitz-Manson classification:
  - Type 1: Single, central fragment, medial canthal ligament intact
  - Type 2: Comminuted central fragment, medial canthal ligament intact
  - Type 3: Severe comminution of central fragment and disrupted medial canthal ligament

### Clinical Presentation

- telecanthus (increased intercanthal distance secondary to medial canthal ligament disruption)
- orbital rim step-off
- similar to nasal fractures (see *Nasal Fractures*, PL30)

### Treatment

- surgical repair to restore intercanthal distance, nasal projection and orbital anatomy

## Zygomatic Fractures

- 3 categories (see Figure 37)
  - fracture restricted to zygomatic arch
  - depressed fracture of zygomatic complex (zygoma)
  - unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone and orbital rim

### Clinical Features

- flattening of malar prominence (view from above)
- pain over fractures on palpation
- numbness in V2 distribution (infraorbital and superior dental nerves)
- palpable step deformity in bony orbital rim (especially inferiorly)
- often associated with fractures of the orbital floor
- ipsilateral epistaxis; trismus (lock jaw)

### Treatment

- if undisplaced, stable and no symptoms, then soft diet; no treatment necessary
- ophthalmologic evaluation if suspected orbital injury
- uncomplicated zygomatic arch fractures can be elevated using Gillies approach: leverage on the anterior part of the zygomatic arch via a temporal incision; stabilization often unnecessary
- ORIF for displaced or unstable fractures of zygomatic complex

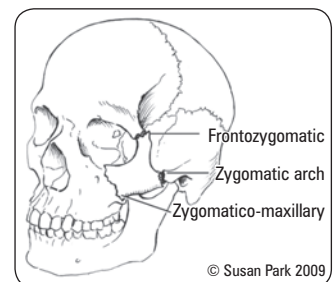


Figure 37. Zygomatic fractures

## Orbital Floor Fractures

- see [Ophthalmology](#), OP42

### Definition

- fracture of floor of orbit ± intact infraorbital rim (see Figure 38)
- may be associated with nasoethmoid fracture

### Etiology

- blunt force to eyeball → sudden increase in intra-orbital pressure (e.g. baseball or fist)

### Clinical Features

- check visual fields and acuity for injury to globe**
- periorbital edema and bruising, subconjunctival hemorrhage
- ptosis, exophthalmos, exorbitism, or enophthalmos
- orbital rim step-offs with possible infraorbital nerve anesthesia
- vertical dystopia (abnormal displacement of the entire orbital cone in the vertical plane); diplopia looking up or down (entrapment of inferior rectus), limited EOM
- orbital entrapment:
  - clinical diagnosis that is a surgical emergency
  - diplopia with vertical gaze; limited EOM
  - severe pain or nausea and vomiting with eye movement
  - requires urgent ophthalmology evaluation and surgical repair

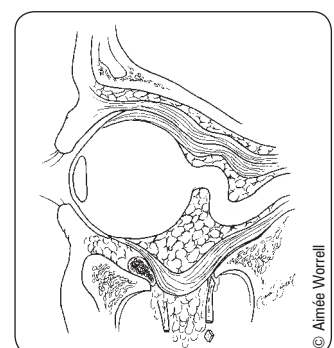


Figure 38. Blow-out fracture

### Investigations

- CT (diagnostic): axial and coronal views
- diagnostic manoeuvre for entrapment is **forced duction** test (pulling on inferior rectus muscle with forceps to ensure full ROM) under anesthesia

### Treatment

- surgical repair indicated if: urgent repair for entrapment, floor defect >1 cm, any size defect with enophthalmos or persistent diplopia (>10 d)
- reconstruction of orbital floor with bone graft or alloplastic material
- ophthalmologic evaluation suggested

### Complications

- persistent diplopia
- enophthalmos

### Superior Orbital Fissure Syndrome

- fracture of SOF causing ptosis, proptosis, anesthesia in V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, VI)
- uncommon complication seen in Le Fort II and III fractures (1/130)
- recovery time reported as 4.8–23 wk following operative reduction of fractures

### Orbital Apex Syndrome

- fracture through optic canal with involvement of CN II at apex of orbit
- symptoms are the same as SOF syndrome plus vision loss
- treatment is urgent decompression of fracture in optic canal or steroids (emergency)



Diplopia can present late in orbital blow-out fractures.

## Breast Surgery

### Breast Reconstruction

- integral part of breast cancer treatment
- two basic methods: implants (1-stage or 2-stage) or autologous tissue (see Table 27)
- may also require breast balancing procedure and nipple areola reconstruction

### Pre-Reconstruction Considerations

- radiation: treatment before and after mastectomy is a relative contraindication to alloplastic reconstruction
- recipient tissue: skin sparing mastectomy allows for the use of implants without tissue expanders (1-stage process)
- donor tissue: limited availability of suitable donor tissue (lack of tissue, scar, previous surgery that interferes with blood supply) may prevent the use of autologous tissue reconstruction
- timing (immediate vs. delayed)
- contralateral breast: may not be possible to reconstruct a breast of the same size or shape as the contralateral breast. Breast reduction or mastopexy may be considered in opposite breast (see Table 28)
- other considerations: patient's age and co-morbidities, prognosis, body weight, characteristics of chest wall and patient's attitude



Patients may require a balancing procedure on contralateral side.

**Table 27. Options for Breast Reconstruction**

Procedure	Definition	Surgical Details	Other Comments
<b>Implant</b>	Use of synthetic material (silicone or saline implants)	<i>With expanders</i> (2 stages): Use tissue expanders before replacement with implants to help facilitate breast ptosis. (see <i>Breast Tissue Expanders</i> , PL33) <i>Without expanders</i> (1 stage): In skin-sparing mastectomy, enough skin is available for immediate placement of implant	Complications: capsular contraction (foreign body reaction to implants), rupture or leakage of implant, increased risk of infection, 35% revision rate over 5 yr
<b>Autologous Tissue</b>	Use of patient's own tissue	Many flap options: DIEP, TRAM, latissimus dorsi, SIEA, SGAP, and IGAP	Offers reduced long-term morbidity and natural consistency
<b>Nipple Areola Reconstruction</b>	Final stage of breast reconstruction	Usually require tattooing for areola reconstruction Local vs. distant flap/graft: 1. Local: fish tail or skate flap most common; these flaps allow simultaneous nipple and areola reconstruction 2. Distant: opposite nipple, earlobe, abdominal skin, costal cartilage, labia	Usually performed 3 mo post-reconstruction

## Breast Tissue Expanders

- types: textured vs. smooth, both with integrated port
- placement: sub-pectoral, total submuscular (pectoral/serratus)
- size: depends on contralateral breast and desired size
  - generally over-expanded to facilitate ptosis
- timing of expansion: begins when wound fully healed (usually 2 wk post-op), and implants are expanded weekly or bi-weekly until complete (up to 3 mo). Expanders are exchanged for implants after another 3 mo for consolidation of expanded skin

## Breast Reduction

- reduction mammoplasty performed for relief of physical symptoms (e.g. shoulder groove, neck pain, back pain, shoulder pain, mastodynia), and to improve breast size and shape
- key steps of procedure:
  - incisions: circular around the areola, vertical from areola incision to infra-mammary fold, along the natural infra-mammary fold
  - removal of fat, breast tissue, and excess skin
  - possible need to move nipple and areola complex to higher position
- complications: infection, hemorrhage, decreased nipple sensation, inability to breast feed, breast/nipple asymmetry, nipple loss (partial or complete), skin loss/necrosis, fat necrosis

## Aesthetic Surgery

### Aesthetic Procedures

Table 28. Aesthetic Procedures

Location	Procedure	Description
Head/Neck	Hair transplants	Aesthetic improvement of hair growth patterns using grafts or flaps
	Otoplasty	Surgical correction of protruding ears
	Brow lift	Surgical procedure to lift low brows
Face	Rhytidectomy	Surgical procedure to reduce wrinkling and sagging of the face and neck. "Face lift"
	Blepharoplasty	Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin $\pm$ fat pads
	Rhinoplasty	Intranasal surgical reconstruction of the nose
	Genioplasty	Chin augmentation via osteotomy or synthetic implant to improve contour
	Lip augmentation	Procedure to create fuller lips and to reduce wrinkles around the mouth using collagen injections, fat transferred from other body parts, or implantable materials
Skin	Chemical peel	Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration
	Dermabrasion	Skin re-surfacing by sanding with a rapidly rotating abrasive tool. Often used to reduce scars, irregular skin surfaces and fine lines
	Laser resurfacing	Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening. Often used to reduce scars and wrinkles
	Injectable fillers	An injectable substance is used to decrease frown lines, wrinkles and nasolabial folds. Substances include collagen, fat, hyaluronic acid and calcium hydroxyapatite
Other	Abdominoplasty	Removal of excess skin and repair of rectus muscle laxity (rectus diastasis). "Tummy tuck"
	Breast augmentation	Surgical breast enhancement with silicone or saline implants (see Figure 39)
	Calf augmentation	Augmentation of calf muscle with implants
	Liposuction	Surgical removal of adipose tissue for body contouring (not a weight loss procedure)
	Mastopexy	Surgical breast lift to elevate breast mound and tighten the skin envelope in ptotic breasts
	Breast reduction	Surgical breast reduction for relief of physical symptoms
	Sclerotherapy	Injection with a sclerosant to treat telangiectasias and varicose veins

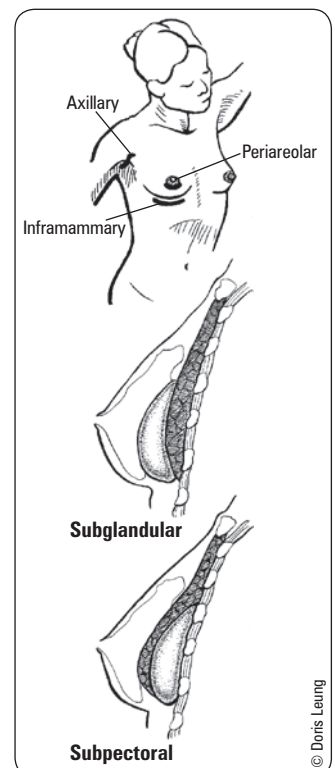


Figure 39. Augmentation mammoplasty: incision lines and implant placement

# Pediatric Plastic Surgery

## Craniofacial Anomalies

Table 29. Pediatric Craniofacial Anomalies

	Definition	Epidemiology	Clinical Features	Treatment
<b>Cleft Lip</b>	Failure of fusion of maxillary and medial nasal processes  M:F = 2:1	1 in 1000 live births (1 in 800 Caucasians, increased in Asians, decreased in Blacks) More common on the left (cleft of left lip/palate in boys has hereditary component)	Classified as incomplete/complete and uni/bilateral 2/3 cases: unilateral, left sided, male	Surgery (3 mo): Millard or Tennison-Randall; corrections usually required later on (esp. for nasal deformity)
<b>Cleft Palate</b>	Failure of fusion of lateral palatine/median palatine processes and nasal septum	Isolated cleft palate: 0.5 per 1000 (no racial variation) F > M	Classified as incomplete/complete and uni/bilateral Isolated (common in females) or in conjunction with cleft lip (common in males)	Special bottles for feeding Speech pathologist Surgery (6-9 mo): Von Langenbeck or Furlow Z-Plasty ENT consult – often recurrent OM, requiring myringotomy tubes
<b>Craniosynostosis</b>	Premature fusion of $\geq 1$ cranial sutures Primary – abnormal suture, no known cause This may limit brain growth perpendicular to the suture and cause compensatory growth parallel to the fused suture	1 in 2000 live newborns; M:F = 52:48 Syndromes include: Crouzon's, Apert's, Saethre-Chotzen, Carpenter's, Pfeiffer's Jackson-Weiss and Boston-type syndromes	Syndromic – assoc. with genetic mutation Secondary (to microcephaly, hyperthyroid, rickets, etc.) Dx: irregular head shape, craniofacial abnormalities, x-ray	Multidisc. team (incl. neurosurg, ENT, genetics, dentistry, peds, SLP) Early surgery prevents secondary deformities $\uparrow$ ICP is an indication for emergent surgery ICU bed may be req'd post-surgically

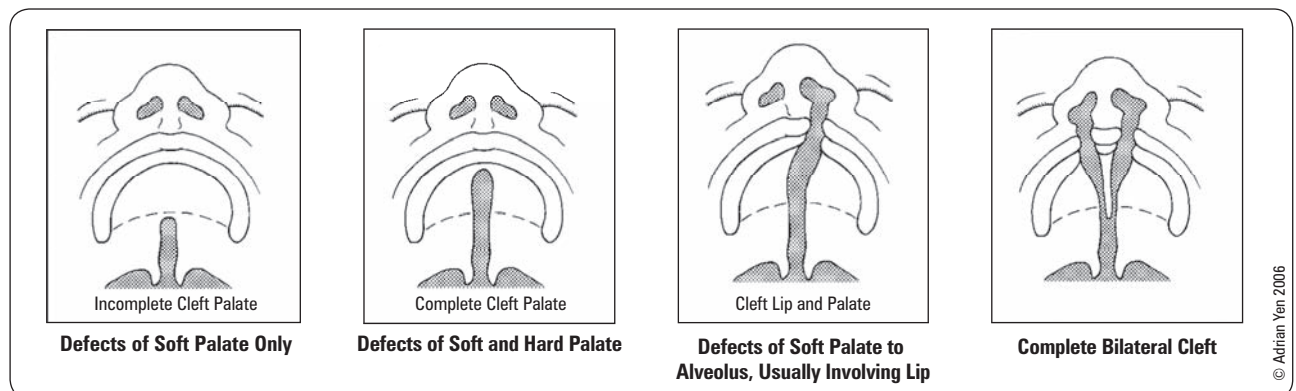


Figure 40. Types of cleft lips and palates

## Congenital Hand Anomalies

Table 30. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

Classification	Example	Features	Treatment
<b>Failure of formation</b>	Transverse absence (congenital amputation)	At any level (often below elbow/wrist)	Early prosthesis
	Longitudinal absence (phocomelia)	Absent humerus Thalidomide-assoc.	
	Radial deficiency (radial club hand)	Radial deviation Thumb hypoplasia M > F	Physiotherapy + splinting Soft tissue release if splinting fails Distraction osteogenesis (Ilizarov) $\pm$ wedge osteotomy Tendon transfer Pollicization
	Thumb hypoplasia	Degree ranges from small thumb with all components to complete absence	Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger
	Ulnar club hand	Rare, compared to radial club hand Stable wrist	Splinting and soft-tissue stretching therapies Soft-tissue release (if above fails) Correction of angulation (Ilizarov distraction)
	Cleft hand	Autosomal dominant Often functionally normal (depending on degree)	First web space syndactyly release Osteotomy/tendon transfer of thumb (if hypoplastic)



**Table 30. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies (continued)**

Classification	Example	Features	Treatment
<b>Failure of differentiation/separation</b>	Syndactyly	Fusion of $\geq 2$ digits 1/3000 live births M:F = 2:1 Classified as partial/complete Simple (skin only) vs. complex (osseous or cartilaginous bridges)	Surgical separation before 6-12 mo of age Usually good result
	Symbrachydactyly	Short fingers with short nails at fingertips	Digital separation (more difficult) Webspace deepening
	Camptodactyly	Congenital flexion contracture (usually at PIP, esp. 5th digit)	Early splinting Volar release Arthroplasty (rarely)
	Clinodactyly	Radial or ulnar deviation Often middle phalanx	None (usually). If severe, osteotomy with grafting
<b>Duplication</b>	Polydactyly	Congenital duplication of digits May be radial (increased in Aborigines and Asians) or central or ulnar (increased in Blacks)	Amputation of least functional digit Usually >1 yr of age (when functional status can be assessed)
<b>Overgrowth</b>	Macroductyly	Rare	None (if mild) Soft tissue/bony reduction
<b>Undergrowth</b>	Brachydactyly	Short phalanges	Removal of non-functional stumps Osteotomies/tendon transfers Distraction osteogenesis Phalangeal/free toe transfer
	Symbrachydactyly (brachysyndactyly)	Short webbed fingers	As above + syndactyly release
<b>Constriction band syndrome</b>	aka amniotic (annular) band syndrome	Variety of presentations	Urgent release for acute, progressive edema distal to band in newborn Other reconstruction is case-specific
<b>Generalized skeletal abnormality</b>	Achondroplasia, Marfan's, Madelung's	Variety of presentations	Treatment depends on etiology

## References

### General Plastic Surgery Concepts

- Britt LD, Trunkley DD, Feliciano DV. Acute care surgery: principles and practice. New York: Springer, 2007.
- Borges AF. The rhombic flap. *Plast Reconstr Surg* 1981;67:458-466.
- Bray DA. Clinical applications of the rhomboid flap. *Arch Otolaryngol* 1983;109:37-42.
- Brown DL, Borschel GH. Michigan manual of plastic surgery. Philadelphia: WB Saunders, 2004.
- Centers, B. Guidelines for the operation of burn centers. Resources for Optimal Care of the Injured Patient, 2006.
- Daver BM, Antia NH, Furnas DW. Handbook of plastic surgery for the general surgeon, 2nd ed. New Delhi: Oxford University Press, 1995.
- Department of Health, Western Australia. Guidelines for use of nanocrystalline silver dressing – Acticoat™. Perth: Health Networks Branch, Department of Health, Western Australia, 2011.
- Diehr S, Hamp A, Jamieson B. Clinical inquiries: do topical antibiotics improve wound healing? *J Fam Pract* 2007;56:140-144.
- Fee WE Jr, Gunter JP, Carder HM. Rhomboid flap principles and common variations. *Laryngoscope*. 1976;86:1706-1711.
- Georgiade GS, Riefkohl R, Levin LS. Georgiade plastic, maxillofacial and reconstructive surgery, 3rd ed. Baltimore: Williams & Wilkins, 1997.
- Gourgiotis S, Villias C, Germanos S, et al. Acute limb compartment syndrome: a review. *J Surg Educ* 2007;64:178-186.
- Greene FL, Page DL, Fleming ID, et al. AJCC cancer staging handbook: from the AJCC cancer staging manual, 6th ed. Springer, 2002.
- Gulleth Y, Goldberg N, Silverman R, Gastman B. What is the best surgical margin for a basal cell carcinoma: a meta-analysis of the literature. *Plast Reconstr Surg* 2010;126:1222-1231.
- Huang CC, Boyce SM. Surgical margins of excision for basal cell carcinoma and squamous cell carcinoma. *Seminars In Cutaneous Med and Surg* 2004;23:167-173.
- Hunt TK, Doherty GM, Way LW, eds. Current surgical diagnosis and treatment, 12th ed. Norwalk: McGraw-Hill, 2006. Chapter: wound healing.
- Janis JE. Essentials of plastic surgery: a UT Southwestern Medical Center handbook. St. Louis: Quality Medical, 2007.
- Larrabee WF Jr, Trachy R, Sutton D, Cox K. Rhomboid flap dynamics. *Arch Otolaryngol* 1981;107:755-757.
- Muangman P, Chuntrasakul, C, Silthram S, et al. Comparison of efficacy of 1% silver sulfadiazine and acticoat for treatment of partial-thickness burn wounds. *J Med Assoc Thailand* 2006;89:953-958.
- Noble J. Textbook of primary care medicine, 3rd ed. St. Louis: Mosby, 2001.
- Ong YS, Samuel M, Song C. Meta-analysis of early excision of burns. *Burns* 2006;32:145-150.
- Plastic Surgery Educational Foundation. Plastic and reconstructive surgery essentials for students. Arlington Heights: Plastic Surgery Educational Foundation, 2007. Available from: [http://www.plasticsurgery.org/medical\\_professionals/publications/Essentials-for-Students.cfm](http://www.plasticsurgery.org/medical_professionals/publications/Essentials-for-Students.cfm).
- Richards AM. Key notes in plastic surgery. Great Britain: Blackwell Science, 2002.
- Salzberg CA, Ashikari AY, Koch RM, et al. An 8-year experience of direct-to-implant immediate breast reconstruction using human acellular dermal matrix (Allo Derm). *Plast Reconstr Surg*. 2011;127:514-524.
- Sermer NB. Practical plastic surgery for non-surgeons. Philadelphia: Hanley & Belfus, 2001.
- Smith DJ, Brown AS, Cruse CW, et al. Plastic and reconstructive surgery. Chicago: Plastic Surgery Educational Foundation, 1987.
- Stone C. Plastic surgery: facts. London: Greenwich Medical Media, 2001.
- Thorne, Charles H. Grabb & Smith's plastic surgery, 6th ed. Lippincott Williams & Wilkins, 2007.
- Townsend CM. Sabiston textbook of surgery – the biological basis of modern surgical practice, 16th ed. Philadelphia: WB Saunders, 2001. Chapter: plastic and reconstructive surgery.
- Wolff K, Johnson RA. Fitzpatrick's color atlas and synopsis of clinical dermatology, 6th ed. McGraw-Hill, 2009.
- Weinzweig J. Plastic surgery secrets. Philadelphia: Hanley and Belfus, 1999.

### Hand

- American Society for Surgery of the Hand. The hand: examination and diagnosis, 3rd ed. Philadelphia: Churchill-Livingston, 1990.
- Beredjikian PK, Bozenika DJ. Review of hand surgery. Philadelphia: WB Saunders, 2004.
- Graham B, Regehr G, Naglie G, Wright J. Development and validation of diagnostic criteria for carpal tunnel syndrome. *J Hand Surg* 2006;31:919.e1-919.e7.

Christine Herrera, Anisha Prasad and Anushi Sivarajah, chapter editors

Maria Jogova and Howard Meng, associate editors

Melini Gupta, EBM editor

Dr. Fran E. Scott, staff editor

<b>Historical Context of Public Health</b> . . . . .	<b>2</b>	<b>Health Services Research</b> . . . . .	<b>17</b>
Public Health Services in Canada		Continuous Quality Improvement (CQI)	
Legislation and Public Health in Canada		Cost Analysis	
<b>Determinants of Health</b> . . . . .	<b>3</b>	<b>Outbreak of Infectious Diseases</b> . . . . .	<b>18</b>
Concepts of Health		Definitions	
Vulnerable Populations		Steps to Control an Outbreak	
Disease Prevention			
Health Promotion Strategies		<b>Environmental Health</b> . . . . .	<b>20</b>
<b>Measurements of Health and Disease in a Population</b> . . . . .	<b>7</b>	Environmental Health Jurisdiction	
<b>Epidemiology</b> . . . . .	<b>7</b>	Risk Assessment	
Effectiveness of Interventions		Air	
<b>Types of Study Design</b> . . . . .	<b>11</b>	Water	
Qualitative vs. Quantitative		Soil	
Quantitative Research Methods		Food	
Observational Study Designs		Heavy Metal Toxicity	
Experimental Study Designs		<b>Occupational Health</b> . . . . .	<b>23</b>
Other Study Designs		Workplace Health Promotion and Protection	
<b>Methods of Analysis</b> . . . . .	<b>14</b>	Workplace Disease Prevention	
Distributions		Workplace Treatment and Rehabilitation	
Data Analysis		Workplace Legislation	
Common Statistical Tests		Taking an Occupational Health History	
Causation		Occupational Hazards	
Assessing Evidence		<b>Appendix – Reportable Diseases</b> . . . . .	<b>25</b>
		<b>References</b> . . . . .	<b>26</b>

For more detail on topics covered in this chapter, use this website as a resource: <http://phprimer.afmc.ca/>

# Historical Context of Public Health

See [Ethical, Legal and Organizational Aspects of Medicine](#), ELOAM17 for *Canada Health Act*

## Definitions

- **population health**
  - health of the population as measured by health status indicators (e.g. life expectancy, low birth weight rates)
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; health care services
  - refers to the prevailing or desired level of health in the population of a specific country/region/subset of population
  - considered to be more complex than the aggregate health status of individuals within a population
- **public health**
  - systematic organized efforts to protect, promote, and restore the health of the public
  - refers to the practices, procedures, institutions, and disciplines required to achieve the desired state of population health
- **public health and preventive medicine** (formerly called community medicine)
  - the postgraduate study of health and disease in the population or a specified community
  - five-year Royal College specialty training
  - goal: to identify and address health problems and evaluate the extent to which health services and others address these issues (<http://rcpsc.medical.org/information/index.php?specialty=110&submit=Select>)

Source: Last JM. *A Dictionary of Epidemiology*. 4th ed. New York: Oxford University Press, 2001

## Public Health Services in Canada

**Mission:** to promote and protect the health of Canadians, and reduce health inequities through leadership, partnership, innovation, and action in public health

- local public health units and services within regional health authorities (in most provinces except Ontario, where local public health units are either autonomous or within local government) provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range from hundreds to thousands of people, covering areas of 15 to 1.5 million km<sup>2</sup>

## Legislation and Public Health in Canada

**Table 1. Legislation and Public Health in Canada**

Federal	Provincial	Municipal (Ontario)
<ul style="list-style-type: none"> <li>• Health Canada               <ul style="list-style-type: none"> <li>▪ Provides health services to First Nations, Aboriginal peoples, the Canadian military, and veterans</li> <li>▪ Approves new drugs and medical devices</li> </ul> </li> <li>• Canadian Food Inspection Agency               <ul style="list-style-type: none"> <li>▪ Monitors food products</li> <li>▪ Deals with animal-related infections</li> <li>▪ Regulates food labeling</li> </ul> </li> <li>• Public Health Agency of Canada (main Government of Canada agency responsible for public health)               <ul style="list-style-type: none"> <li>▪ An independent body created to strengthen public health capacity</li> <li>▪ Focuses on preventing chronic diseases, preventing injuries, and responding to public health emergencies and infectious disease outbreaks</li> <li>▪ Oversees immigration screening, protects Canadian borders (e.g. airport health inspection)</li> <li>▪ Liases with the World Health Organization (WHO) on global health issues</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Legislation is in the form of Acts and Regulations</li> <li>• Each province has its own Public Health Act or equivalent (e.g. the Health Protection and Promotion Act in Ontario)</li> <li>• Designates the creation of geographic areas for the provision of public health services</li> <li>• Gives powers to the Chief Medical Officer of Health to control public health hazards</li> <li>• Specifies infectious diseases to be reported to public health units by physicians, laboratories, and hospitals (see <i>Appendix</i>, PH25)</li> <li>• Has the ability to mandate programs that address public health issues, environmental health, and chronic disease prevention</li> </ul>	<ul style="list-style-type: none"> <li>• Local boards of health deliver programs mandated by provincial legislation</li> <li>• Boards of health are responsible for the delivery of most public health services, such as:               <ul style="list-style-type: none"> <li>▪ Infectious disease control, including the follow-up of reported diseases and management of outbreaks</li> <li>▪ Inspection of food premises including those in hospitals, nursing homes, and restaurants</li> <li>▪ Family health services including pre-conception, preschool, school-aged, and adult health programs</li> </ul> </li> <li>• Tobacco control legislation enforcement</li> <li>• Assessment and management of local environmental health risks</li> <li>• Collection and dissemination of local health status reports</li> <li>• Public dental health services to children</li> <li>• By-laws may be approved by municipal governments to facilitate public health issues</li> </ul>



The AFMC Primer on Population Health is the core text for the MCC and is available as an online resource on the AFMC website.  
Source: <http://phprimer.afmc.ca>



For the LMCC exam, it is recommended that you also read all of Chapter 15 in Shah CP. *Public health and preventive medicine in Canada*, 5th ed. Toronto: Elsevier, 2003.

Topics covered include:

- Primary, secondary, tertiary and quaternary health care
- Physician remuneration, organization of primary care, new model of primary health care
- Services of other health care professionals: nurses, dentists, chiropractors, podiatrists, optometrists, midwives, pharmacists, and alternative health care providers
- Hospitals and acute care facilities
- Local public health units/ departments: communicable disease control, women's health and maternal and child health, health promotion, dental health, environmental health, population health assessment and health surveillance
- Home care
- Palliative care
- Services for mental illnesses
- Services for cancer patients
- Services for persons with special needs
- Voluntary agencies
- Self-help groups
- Telehealth



### Historical Perspective

Over the last century, Public Health has evolved through three main epidemiological phases:

- **Infectious diseases:** controlled in the more developed world but an issue in less developed countries (e.g. polio, malaria)
- **Chronic diseases:** chronic diseases and other noncommunicable conditions have increased morbidity and mortality (e.g. heart disease and cancer due to risk factors and/or exposures)
- **Re-emerging infectious diseases:** new or re-emergent infections emerge due to unfamiliar or new pathogens, inefficient or inappropriate antibiotic use, travel, and global warming (e.g. HIV, drug resistant TB and malaria)



### Five Core Functions for All Public Health Units

- Population health assessment
- Health, injury, and disease surveillance
- Health promotion
- Disease and injury prevention
- Health protection

# Determinants of Health



## Medical Officer of Health (MOH) (Ontario)

- May be called "Medical Health Officer" (MHO) in other provinces
- Appointed to each public health unit by the board of health
- Held by a licensed physician with public health training
- Responsibilities include:
  - Collection and analysis of epidemiological data
  - Occupational and environmental health surveillance
  - Implementation of health programs, including:
    - counseling
    - family planning services
    - parenting programs, prenatal courses
    - preschool and school health services
    - disease screening programs
    - tobacco use prevention programs
    - nutrition services to schools and seniors' centres
- The Medical Officer of Health can require an individual/premise/agency to take or refrain from any action due to a public health hazard



## Chief Public Health Officer of Canada

- Responsible for the Public Health Agency of Canada and reports to the Minister of Health
  - As the federal government's lead public health professional, provides advice to the Minister of Health and Government of Canada on health issues
  - Collaborates with other governments, jurisdictions, agencies, organizations, and countries on health matters
  - Communicates public health information to health professionals, stakeholders, and the public
  - In an emergency, such as an outbreak or natural disaster, provides direction to Public Health Agency staff, including medical professionals, scientists, and epidemiologists, as they plan and respond to the emergency
- Source: Public Health Agency of Canada. <http://www.phac-aspc.gc.ca/cpho-acsp/cpho-acsp-role-eng.php>



## Definitions of Health

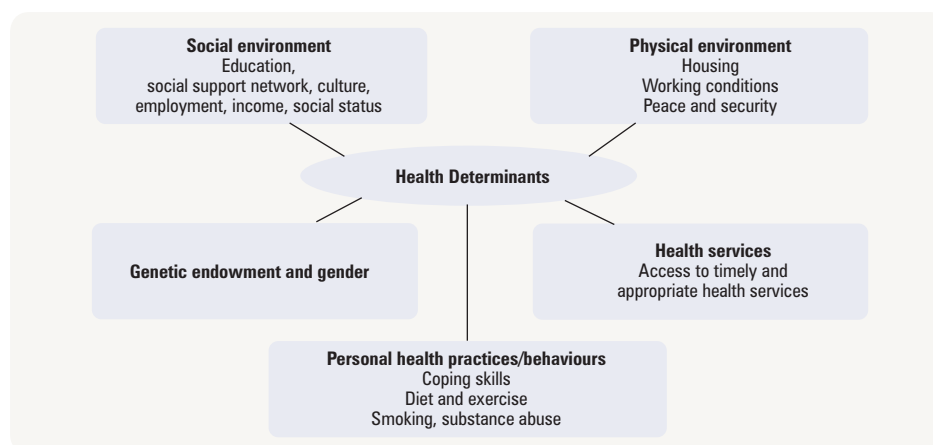
- First multidimensional definition of health, as defined by the WHO in 1948: "A complete state of physical, mental and social well being and not merely the absence of illness"
- WHO updated the definition (socio-ecological definition) of health in 1986: "The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities"
- Other definitions of health have since been proposed that incorporate other dimensions of health (e.g. "Health is a social, economic, and political issue and above all a fundamental human right" – The People's Charter for Health)

## Concepts of Health

- **disease:** abnormal, medically-defined changes in the structure or function of the human body
- **illness:** an individual's experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles
- **impairment:** any loss or abnormality of psychological, physiological, or anatomical structure or function
- **disability:** any restriction or lack of ability to perform an activity within the range considered normal for a human being
- **handicap:** the disadvantage for an individual arising due to impairment and disability
  - limits or prevents the fulfillment of an individual's normal role as determined by society and depends on age, sex, social, and cultural factors
  - changes the individual's relationship with the physical and social environment
- **health equity:** when all people have "the opportunity to attain their full health potential" and no one is "disadvantaged from achieving this potential because of their social position or other socially determined circumstance." Differs from health equality
- **health equality:** defined as where populations have equal or similar health status. Health inequities are those which are considered unjust and/or preventable

## Determinants of Health

- 1974: the Honourable Marc Lalonde, federal Minister of Health, presented the health field concept entitled *A New Perspective on the Health of Canadians* which included four areas that interact to determine health: human biology, environment, lifestyle, and health care
- since then this concept has been expanded to include numerous determinants of health (see below)



**Figure 1. Population health model**

Adapted from Dahlgren G, Whitehead M. *Policies and Strategies to Promote Social Equity in Health*. Stockholm: Institute of Future Studies, 1991

## Vulnerable Populations

**Table 2. Health Determinants of Vulnerable Populations**

	Definition	Psychosocial/ Socioeconomic	Physical Environment	Individual Behaviour	Population-Specific Interventions
<b>Aboriginal Peoples</b>	Four specific groups: First Nations Status Indians (registered under the <i>Indian Act</i> ), non-Status Indians, Métis, and Inuit	Low income Family violence Low education status Unemployment Homelessness Longer length of disability	Crowded housing Inefficient ventilation Environmental toxins (botulism) TB declining but prevalence higher than rest of population	Smoking Substance misuse Excessive gambling Poor nutrition Sedentary lifestyle High BMI High risk sexual behaviours	Mental health awareness Aboriginal-specific diabetes initiatives Substance abuse treatment programs

**Table 2. Health Determinants of Vulnerable Populations** (continued)

	Definition	Psychosocial/ Socioeconomic	Physical Environment	Individual Behaviour	Population-Specific Interventions
<b>Seniors</b>	Individuals >65 yr	Elder abuse Lack of emotional support	Low hazard tolerance Institutionalization	Inactivity Polypharmacy Medical co-morbidities	Aging in place of choice Falls and injury prevention Mental health promotion Preventing abuse and neglect
<b>Children in Poverty</b>	Based on Low Income Cut Offs (LICO) LICO is an income threshold below which a family will likely devote a larger share of its income on the necessities of food, shelter and clothing than the average family	Low income Family dysfunction Lack of educational opportunities	Housing availability Unsafe housing Lack of recreational space	Poor supervision Food insecurity High risk behaviours	Improvements in family income most significant Early childhood education
<b>People with Disabilities</b>	Includes impairments, activity limitations, and participation restrictions	Low income Low education status Discrimination	Institutionalization Barriers to access Transportation challenges	Substance misuse Poor nutrition Inactivity Dependency for ADLs	Transportation support Multidisciplinary care Unique support for individuals with specific disabilities (e.g. Trisomy 21)
<b>New Immigrants</b>	Person born outside of Canada who has been granted the right to live in Canada permanently by immigration authorities	Access to community services Cultural perspectives	Diseases and conditions in country of origin (e.g. smoke from wood fires, incidence of TB, etc.)	Employment, ESL Healthy Newcomer Effect (health worsens over time to match that of the general population) Cultural or religious expectations	Women's health Mental health Infectious diseases (syphilis blood test, CXR, HIV) Dental and vision screening Vaccinations Cancer screening
<b>Homeless Persons</b>	An individual who lacks permanent housing	Low income Mental illness	Exposure to temperature extremes Infections such as West Nile Virus	Substance misuse Violence	Safe housing Addictions support Mental health
<b>Refugee Health</b>	Forced to flee country of origin because of a well-founded fear of persecution and given protection by the Government of Canada  <i>Refugee claimant:</i> Arrive in Canada and ask to be considered refugee	Post-traumatic stress disorders Depression Adjustment problems IFH (Interim Federal Health) for refugee claimants, health coverage 1 yr for medical necessities, specifically does not cover screening or preventative care Additionally IFH will restrict coverage for individuals from designated countries of origin (DCO) whose applications were placed after Dec 15, 2012	Diseases and conditions in country of origin (e.g. malaria, TB, onchocerciasis, etc.) Direct and indirect effects of war	Employment ESL Longstanding prior lack of access to health care (chronically neglected problems) Cultural or religious expectations	Vaccinations Women's health Mental health Infectious diseases Dental and vision screening Political advocacy

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population



#### Determinants of Health

- Income and social status
- Social support networks
- Education and literacy
- Employment and working conditions
- Social environment
- Physical environment
- Personal health practices and coping skills
- Healthy child development
- Biology and genetic endowment
- Health services
- Gender
- Culture

Source: Public Health Agency of Canada



#### New Immigrants to Canada

- Mandatory medical exams on entry to Canada by a designated medical practitioner:
  - Complete medical examination for all persons of all ages
  - Chest x-ray and report for persons 11 yr of age and over
  - Urinalysis for persons 5 yr of age and over
  - Syphilis serology for persons 15 yr of age and over
  - HIV testing for applicants 15 yr of age and over, as well as for those children who have received blood or blood products, have a known HIV-positive mother, or have an identified risk. An ELISA HIV screening test should be done for HIV 1 and HIV 2
  - Serum creatinine if the applicant has hypertension (resting blood pressure greater than 140/90 mmHg), a history of treated hypertension, diabetes, autoimmune disorder, persistent proteinuria, or kidney disorder

Citizenship and Immigration Canada. Handbook.  
<http://www.cic.gc.ca>



#### Example of Primary Prevention: Gardasil Vaccine and its Efficacy in the Prevention of Cervical Cancer

Gardasil® is a quadrivalent HPV vaccine covering strains 6,11,16,18. The efficacy of Gardasil® was studied in 4 randomized, double-blind, placebo controlled trials on females between 16 and 26 yr of age and was found to prevent nearly 100% of precancerous cervical changes for up to 4 yr after vaccination.



#### Example of Primary Prevention: The Obesity Prevention Campaign by the Ontario Medical Association (OMA)

The OMA campaign has involved calls for early action on menu labeling from leaders in the restaurant field, lobbying the provincial government to enact legislation requiring calorie contents to be listed on menus at chain restaurants and school cafeterias, and an education campaign to inform the public about the impact of caloric intake on weight gain and obesity.

Source: Ontario Medical Association. <https://www.oma.org/HEALTHPROMOTION/OBESITY/Pages/default.aspx>

## Disease Prevention

### Disease Prevention Strategies

- measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

### Primary Prevention

- implemented to prevent disease from occurring
- immunization programs exist in most countries to address major causes of pediatric morbidity and mortality that are preventable by vaccines, e.g. measles, diphtheria, pertussis, tetanus, polio, and tuberculosis (not routine in Canada or the U.S.)



- additional immunizations are offered in Canada depending on jurisdiction: mumps, rubella, rotavirus, hepatitis B, *Haemophilus influenzae* type B, varicella, HPV, conjugated pneumococcal and meningococcal vaccines (see [Pediatrics, P3](#))

### Secondary Prevention (Screening)

- presumptive identification (not diagnosis) of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly
- **types of screening**
  - mass screening: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
  - selective screening: screening of a specific subgroup of the population at risk for a disease (e.g. mammography in women >50 yr old)
  - multiphasic screening: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)

**Table 3. Ideal Criteria for Screening Tests**

Disease	Test	Health Care System
Causes significant suffering and/or death Natural history must be understood Must have an asymptomatic stage that can be detected by a test Early detection and intervention must result in improved outcomes Incidence is not too high or too low	High specificity and sensitivity Safe, rapid, easy, relatively inexpensive Acceptable to providers and to population	Adequate capacity for reporting, follow-up, and treatment of positive screens Cost effective Sustainable program Clear policy guidelines

### Tertiary Prevention

- treatment and rehabilitation of disease after it has been diagnosed so as to prevent progression and permanent disability (e.g. HbA1c, eye, and foot monitoring for diabetes)

## Health Promotion Strategies

**Table 4. Disease Prevention versus Health Promotion Approach**

Disease Prevention	Health Promotion
Health = absence of disease	Health = positive and multidimensional concept
Medical model (passive role)	Participatory model of health
Aimed mainly at high-risk groups in the population	Aimed at the population in its total environment
Concerns a specific pathology	Concerns a network of issues
One-shot strategy	Diverse and complementary strategies
Directive and persuasive strategies	Facilitating and enabling approaches
Directive measures enforced in target groups	Incentive measures offered to the population
Focused mostly on individuals and groups of subjects	Focused on a person's health status and environment
Preventive programs considered the affairs of professional groups from health disciplines	Non-professional organizations, civic groups, local, municipal, regional, and national governments necessary for achieving the goal of health promotion

Source: Shah CP. Public Health and Preventive Medicine in Canada. Toronto: Elsevier, 5th edition, 2003

### Healthy Public Policy

- characterized by an explicit concern for health and equity in all areas of policy and by an accountability for health impact
- main aim: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- government sectors must take into account health as an essential factor when formulating policy and should be accountable for the health consequences of their policy decisions
- methods:
  - fiscal: imposing additional costs (e.g. taxes on tobacco and alcohol)
  - legislative: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  - social: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)

### Community Development

- process of community members identifying issues and problems affecting their community and subsequently developing the skills and capacity to implement change



#### Disease Prevention Strategies

- **Primary:** before disease occurs (e.g. immunizations, seatbelt use, smoking cessation programs for lung cancer prevention)
  - **Secondary:** early detection of disease (e.g. mammography, routine Pap smears)
  - **Tertiary:** treatment and rehabilitation of existing disease (e.g. ACE inhibitor for hypertension)
- Within these three stages of prevention there can be both:
- **Passive prevention:** measures that operate without the person's active involvement (e.g. airbags in cars)
  - **Active prevention:** measures that a person must do on their own (e.g. wearing a seatbelt)



#### Ottawa Charter for Health Promotion (1986)

- Governments and health care providers should be involved in a health promotion process that includes:
  - Building healthy public policy
  - Creating supportive environments
  - Strengthening community action
  - Developing personal skills
  - Re-orienting health services



#### Jakarta Declaration on Health Promotion into the 21st Century (WHO 1997)

- Reiterated the commitment to health promotion
- First of the health promotion conferences to involve the private sector
- Formally cited poverty as the greatest threat to health
- Priorities for health promotion:
  - Promote social responsibility for health
  - Increase investments for health development
  - Consolidate and expand partnerships for health
  - Increase community capacity and empower the individual
  - Secure an infrastructure for health promotion



#### Labonte's Model of Community Development

- Personal empowerment
- Small group development
- Community organization
- Coalition advocacy
- Political action



#### 4 Ps Influencing Health Marketing

- Product:** good health
- Price:** what a person must give up if he or she accepts the product "pursuing good health"
- Place:** the distribution channels used to reach the consumer (e.g. distributing pamphlets at the doctor's office)
- Promotion:** the way in which the product is promoted to the consumer



### Community-Based Prevention

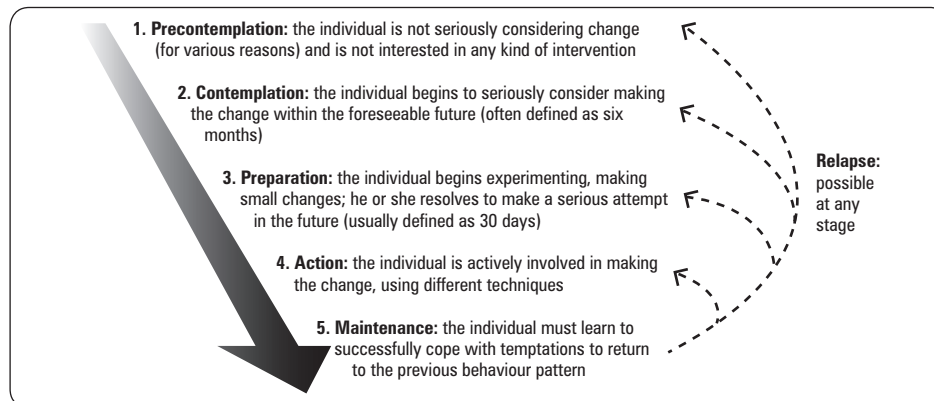
- public health service (prevention or promotion) focused on an entire community as opposed to only high-risk groups/individuals
- “community-based approaches” are population-based multifactorial initiatives that make use of community organization and social marketing to elicit change at the community level (e.g. *Saskatoon's In Motion program* – see sidebar)
- numerous preventable risk factors are addressed by multiple health promotion strategies

### Health/Social Marketing

- application of the principles of commercial marketing to promote healthy changes
- involves target group analysis and segmentation of the market for specific messages and promotion strategies
- employed by both the health system (e.g. pamphlets providing health information about HIV) and by industry (e.g. in medication advertisements)

### Behaviour Change

- health education serves to:
  - increase knowledge and skills
  - encourage positive behaviour changes and discourage unhealthy choices
- health education is an important component of eliciting behaviour change
- behaviour is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community
- **Health Belief Model** (1975)
  - behaviours undertaken by individuals in order to remain healthy are a function of a set of interacting beliefs
  - beliefs include an individual's perception of his or her susceptibility to a disease, the severity of the disease, and the benefits and costs of health-related actions
  - beliefs are modified by socio-demographic and psychosocial variables
  - individuals must believe that the action will have positive consequences
  - individuals must be in a state of readiness
  - behaviour can be stimulated by cues to action, which are specific events that can encourage preventive health decisions and actions (e.g. physician recommendation, public advertising)
- **Stages of Change Model**
  - provides a framework in which the Health Belief Model is applied to facilitating behaviour change (e.g. quitting smoking)



**Figure 2. Stages of change model**

Source: Prochaska JO, DeClement CC, and Norcross JC. In Search of How People Change. Applications to Addictive Behaviours. Am Psychol 1992;47:1102-1114

### Risk Reduction Strategies

- **risk reduction:** lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
- **harm reduction:** tolerance of some degree of risk behaviour, while aiming to minimize the adverse outcomes associated with these behaviours (e.g. needle exchange programs)

### Innovation-Diffusion Theory

- theory that describes the process by which health promotion efforts spread in populations
- aims to identify the most effective methods of health promotion within a population
- **Roger's diffusion theory** illustrates the following hierarchy within populations:
  - innovators
  - early adopters (community leaders)
  - early majority
  - late majority
  - laggards



**Saskatoon's In Motion** is a community-based strategy to increase physical activity through collaborative community efforts. 98% of all Saskatoon schools have now committed to meeting In Motion goals, including at least 30 min of daily physical activity per child. Elementary schools also report that students are active on one additional day per week compared to pre-program activity levels. In Motion is viewed as a best practice strategy and is now being implemented in communities and provinces across Canada.

Chief Public Health Officer's Report, 2009.



#### Example of Harm Reduction Strategy Summary of Findings from the Evaluation of a Pilot Medically Supervised Safer Injecting Facility

CMAJ 2006;175:1399-1404

**Background:** This study discusses the outcomes among a population of illicit injection drug users (IDUs) after initiating a supervised safe injecting facility in Vancouver, September 2003. Legal exemption by the Canadian government was granted such that an evaluation of its results be conducted over a 3 yr period.

**Study Population:** IDUs of the Vancouver area were allowed to inject previously obtained illicit drugs under the supervision of nurses and physicians. IDUs were offered addiction counseling and supports for appropriate community resources. A random sample of 670 IDUs was recruited and monitored from Dec 2003-July 2004.

**Results:** Characteristics of IDUs who used the safe injecting facility included age <30 yr, history of public drug use, homelessness, daily heroin and/or cocaine injection, and recent history of overdose. Mean measures of public order problems were taken 6 wk before and 12 wk after initiation of the safer injection facility. It was found that the mean number of IDUs injecting daily in public, along with the mean number of publicly discarded syringes were reduced by approximately half.

**Conclusions:** Overall it has been found that the safer injection facility in Vancouver has been successful in attracting IDUs at increased risk of HIV, overdose, and public injection of substances. This has resulted in lower incidences of public drug use, publicly discarded syringes and sharing of needles. Other studies associated with this one have demonstrated that there has been no increase in the drug dealing, drug related crimes, or rates of new IDUs in the area surrounding the safer injecting facility.



#### Characteristics of Innovations that Influence Positive Adaptability of the Change

- Simple
- Workable
- Reversible
- Flexible
- Advantageous
- Cost effective
- Low risk
- Compatible with value systems

# Measurements of Health and Disease in a Population

## Life Expectancy

- the expected number of years that an individual will live based on standardized death rates for the population
- usually qualified by country, gender, and age

## Crude Death Rate

- mortality rate from all causes of death per 1000 in the population

## Age Standardized Rate

- adjustment of the crude rate of a health-related event using a "standard" population
- standard population is one with a known number of persons in each age and sex group (e.g. the 1991 census data for Canada using 5-yr age intervals for males and females)
- standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time)

## Standardized Mortality Rate

- the ratio of the observed (actual) number of deaths to the expected number of deaths for a group (e.g. age, race, gender, etc.)
- useful for comparing populations that are significantly different in some aspect (e.g. the causes of death in more and less developed countries)

## Infant Mortality Rate (IMR)

- number of deaths among children under 1 yr of age reported during a given time period divided by the number of live births reported during the same time period and expressed per 1000 live births per year

## Maternal Mortality Rate (MMR)

- number of deaths of women during pregnancy and due to puerperal causes per 100,000 live births per year

## Proportional Mortality Ratio (PMR)

- proportion of all deaths in a specified population over a given period of time attributable to a specific cause
  - each cause is expressed as a percentage of all deaths, with the sum of all causes adding to 100%

## Potential Years of Life Lost (PYLL)

- calculated for a population using the difference between the actual age at death and a standard/expected age at death
- increased weighting of mortality at a younger age

## Disability Adjusted Life Year (DALY)

- quantitative indicator of the burden of diseases that reflects the total amount of disability-free life years lost
- includes loss from premature mortality and loss due to a degree of disability over a specific period of time; these disabilities can be physical or mental

## Quality Adjusted Life Year (QALY)

- a value from 0 to 1 assigned to a yr of life based on perceived quality of life; a yr in "perfect" health is considered equal to 1 QALY, the value of a yr in ill health would be lowered based on the burden of disease
- it is possible to have "states worse than death" for example QALY <0 for extremely serious conditions



### Top 5 Causes of Mortality in Canada, 2012, by Sex

#### Female

- Cancer
- Heart disease
- Stroke
- COPD/chronic lower respiratory disease
- Alzheimer's

#### Male

- Cancer
- Heart disease
- Accidents
- Stroke
- COPD/chronic lower respiratory disease

Source: Statistics Canada. *CANSIM*, 2012. table 102-0561 and 102-0562 and catalogue no.84-215-X.

# Epidemiology



## Population

- a collection of individuals who share a common trait (most commonly applied to a geographic area but it could be another factor such as ethnic group)

### Sample

- a selection of individuals from a population or set of observations
- types:
  - random: all are equally likely to be selected
  - systematic: an algorithm is used to select a subset
  - stratified: separate representations of more than one subgroup
  - cluster: grouped in space/time to reduce costs
  - convenience: non-random inclusion, usually volunteers

### Sample Size

- sample size contributes to the statistical precision of the observed estimate
- increasing the sample size decreases the probability of type I and type II errors (see PH14)

### Bias

- non-random error leading to a deviation of inferences or results from the truth
- any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth
  - **lead-time:** time between early diagnosis with screening and when diagnosis would have been made without screening
  - **lead-time bias:** over-estimation of survival when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening (see Figure 3)
  - **incidence-prevalence bias:** when prevalent cases include long-term survivors who have a better prognosis than some incident cases
  - **length-time bias:** overestimation of the survival time due to the sampling of prevalent as opposed to incident cases
    - ♦ selection of prevalent cases will favour the over-inclusion of longer-living cases rather than newly-diagnosed incident cases, some of whom may have short survival times
  - **sampling bias:** occurs with the selection of a sample that does not truly represent the population
    - ♦ sampling procedures should be chosen to prevent or minimize bias
  - **recall bias:** when individuals with a disease are more prone to recalling or believing they were exposed to a possible causal factor than those who are free of disease

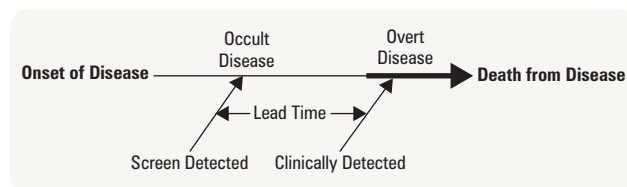


Figure 3. Lead time bias

### Confounder

- a variable that is related to both the exposure and outcome but is not measured or is not distributed equally between groups
- distorts the apparent effect of an exposure or risk because it may not be possible to separate/control for the contribution of a single causal factor to an effect (e.g. late maternal age could be a confounder in an investigation of birth order >4 and risk of developing Trisomy 21)

### Prevalence

- total number of cases in a population over a defined period of time (see sidebar)
- two forms of prevalence
  - **point prevalence:** attempts to measure the frequency of all disease at one specific point in time, therefore knowledge of the time of onset of disease is not required
  - **period prevalence:** measure constructed from prevalence at a point in time, plus new cases and recurrences over a defined period of time
- depends on **incidence rate** (see sidebar) and disease duration from onset to termination (cure or death)
- favours the inclusion of chronic over acute cases and may be used to present a biased picture of the disease
- prevalence studies are cross-sectional and cannot be used for causal inferences
- prevalence figures are useful for determining the extent of a disease and can aid in the rational planning of facilities and services

### Sensitivity

- proportion of people with disease who are correctly identified by a positive test

### Specificity (refer to sidebar)

- proportion of people without disease who are correctly identified by having a negative test



#### Incidence and Prevalence

**Incidence** =  $\frac{\text{number of new cases of disease in a time interval}}{\text{total population at risk} \times [\text{per unit population (e.g. 100 000)}]}$   
(measures the rate of new infections)

**Prevalence** =  $\frac{\text{number of existing cases of disease at a point in time}}{\text{total population} \times [\text{per unit population (e.g. 100 000)}]}$   
(measures the frequency of disease at a point in time)



**SPIN:** use a **SP**ecific test to rule **IN** a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive.

**SNOUT:** use a **SEN**sitive test to rule **OUT** a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative.

TP = True positive TN = True negative FP = False positive FN = False negative

		Disease	
		Present	Negative
Test Result	Positive	TP	FP
	Negative	FN	TN

#### Likelihood Ratio (LR)

- Likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
- LR+ indicates how much the probability of disease increases if the test is positive
- LR- indicates how much the probability of disease decreases if the test is negative

$$LR+ = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{[TP/(TP+FN)]}{[FP/(TN+FP)]}$$

$$LR- = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{[FN/(TP+FN)]}{[TN/(TN+FP)]}$$

#### Positive Predictive Value (PPV)

- Proportion of people with a positive test who have the disease

$$PPV = \frac{TP}{TP + FP}$$

#### Negative Predictive Value (NPV)

- Proportion of people with a negative test who are free of disease

$$NPV = \frac{TN}{TN + FN}$$

#### Pre-test Probability

- An estimate of the likelihood a particular patient has a given disease based on known factors such as clinical assessment prevalence of disease In the population. Together with a post-test probability this can be used to interpret a diagnostic test or a series of tests

$$\text{Pre-test Odds} = \frac{\text{Prevalence}}{1 - \text{Prevalence}}$$

#### Post-test Probability

- A revision of the probability of disease after a patient has been examined or a diagnostic test has been conducted
- Calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests and Bayes' theorem
- The post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
- After each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

$$\text{Post-test Odds} = \text{Pre-Test Odds} \times \text{LR}$$

$$\text{Post-test Probability} = \frac{\text{Post-test odds}}{\text{Post-test odds} + 1}$$

#### Intention-To-Treat (ITT)

- a strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the requirements of that group
- this is to limit the bias introduced by issues of compliance and to simulate real world situations in which not all patients/providers adhere to the study allocation protocol

#### Relative Risk (RR)

- ratio of the incidence of a health outcome among the exposed population to the incidence of the health outcome in the non-exposed population

$$\text{Relative Risk (RR)} = \frac{PPV}{1 - NPV} = \frac{[TP/(TP+FP)]}{[FN/(TN+FN)]}$$

#### Attributable Risk (AR)

- rate of a health outcome attributable to a hypothetical risk factor for that outcome
- [incidence in exposed population] - [incidence in non-exposed]
- attributable risk assumes causation

$$\text{Attributable Risk} = PPV - (1 - NPV) \\ = [TP/(TP+FP)] - [FN/(TN+FN)]$$

		Advanced Neoplasia	
		Present	Negative
Test Result	Positive	68	147
	Negative	216	2234
	Total	284	2381

$$\text{Sensitivity} = 68/284 = 23.9\%$$

$$\text{Specificity} = 2234/2381 = 93.8\%$$

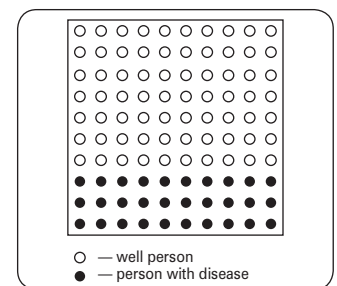
$$LR+ = \frac{0.239}{1 - 0.938} = 3.85$$

$$LR- = \frac{1 - 0.239}{0.938} = 0.81$$

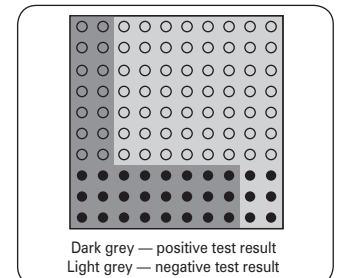
$$PPV = \frac{68}{(68 + 147)} = 31.6\%$$

$$NPV = \frac{2234}{(2234 + 216)} = 91.2\%$$

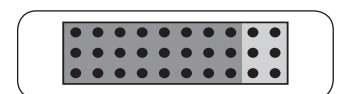
**Figure 4. Understanding sensitivity and specificity**



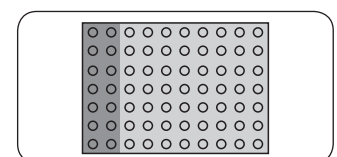
**Figure 4a. Hypothetical population**



**Figure 4b. Results of diagnostic test on hypothetical population**



**Figure 4c. Sensitivity of test (e.g. 24/30 = 80% sensitive)**



**Figure 4d. Specificity of test (e.g. 56/70 = 80% specific)**

Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain. *BMJ* 2003;327:716-719

**Figure 5. Clinical epidemiology definitions and practical example using FOBT testing in advanced colon cancer**

### Pre-test Probability

- an estimate of the likelihood a particular patient has a given disease based on known factors

### Post-test Probability

- a revision of the probability of disease after a patient has been interviewed and examined
- calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests, and Bayes' theorem
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
  - after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

Numbers from Collins J, Lieberman D, Durbin T, Weiss D. Accuracy of Screening for Fecal Occult Blood on a Single Stool Sample Obtained by Digital Rectal Examination: A Comparison with Recommended Sampling Practice. *Ann Intern Med* 2005;142:81-85

		Disease (e.g. lung CA)		
		Present	Absent	Total
Exposure (e.g. smoking)	Present	A	B	A + B
	Absent	C	D	C + D
	Total	A + C	B + D	A + B + C + D

**Case-Control Study**

$$\text{odds ratio (OR)} = \frac{A}{B} \div \frac{C}{D} = \frac{A \times D}{B \times C}$$

**Cohort Study**

$$\frac{A}{A+B} = \text{incidence rate of disease in smokers} \quad \frac{C}{C+D} = \text{incidence rate of disease in non-smokers}$$

$$\text{relative risk (RR)} = \frac{A}{A+B} \div \frac{C}{C+D} \quad \text{attributable risk (AR)} = \frac{A}{A+B} - \frac{C}{C+D}$$


Sensitivity and specificity are characteristics of the test.

LR depends on the test characteristics, not the prevalence.

PPV and NPV depend on the prevalence of the disease in the population.

Figure 6. Results tabulation by study design

## Effectiveness of Interventions

### DEFINITIONS

#### Relative Risk Reduction (RRR)

- proportional reduction in rates of adverse outcomes between experimental and control participants in a trial

#### Absolute Risk Reduction (ARR)

- absolute arithmetic difference in rates of adverse outcomes between experimental and control participants in a trial
- it is hypothesized that events will occur more often in control group than in experimental group where the intervention is protective (e.g. a vaccine)

#### Absolute Risk Increase (ARI)

- absolute arithmetic difference in rates of adverse outcomes between control and experimental participants in a trial
- it is hypothesized that events will occur more often in experimental group than in control group when the intervention is harmful (e.g. alcohol excess)

#### Number Needed to Treat (NNT)

- number of patients who need to be treated to achieve one additional favourable outcome
- only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility, etc. of intervention)
  - a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

#### Number Needed to Harm (NNH)

- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

#### Adherence (formerly compliance)

- degree to which a patient follows a treatment plan



#### Equations to Assess Effectiveness

CER = control group event rate  
 EER = experimental group event rate  
 $RRR = (CER - EER)/CER$   
 $ARR = CER - EER$   
 $ARI = EER - CER$   
 $NNT = 1/ARR$   
 $NNH = 1/ARI$



#### Beware:

Do not be swayed by a large RRR, as it may appear to be large if event rate is small to begin with. In these cases ARR is more important (e.g. a drug which lowers an event which occurs in 0.1% of a population to 0.05% can boast a RRR of 50%, and yet the ARR is only 0.05%, which is not nearly as impressive).

### Effectiveness, Efficacy, Efficiency

- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - **efficacy:** the extent to which a specific intervention produces a beneficial result under ideal conditions
    - ♦ ideally, based on the results of a randomized control trial (the theoretical impact)
  - **effectiveness:** measures the benefit of an intervention under usual conditions of clinical care
    - ♦ considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
  - **efficiency:** a measure of economy of an intervention with known effectiveness
    - ♦ considers the optimal use of resources (e.g. money, time, personnel, equipment, etc.)



## Types of Study Design

### Qualitative vs. Quantitative

Table 5. Qualitative vs. Quantitative Study Designs

Qualitative	Quantitative
Generates hypothesis (Why? What does it mean?)	Tests hypothesis (What? How much/many?)
Inductive (specific to general): "bottom up" Observation → pattern → tentative hypothesis → theory	Deductive (general to specific): "top down" Theory → hypothesis → observation → confirmation
Sampling approach to obtain representative coverage of ideas or concepts	Sampling approach to obtain representative coverage of people in the population
Narrative: rich, contextual, and detailed information from a small number of participants	Numeric: frequency, severity, and associations from a large number of participants

Source: Adapted from <http://phprimer.afmc.ca>

### Quantitative Research Methods

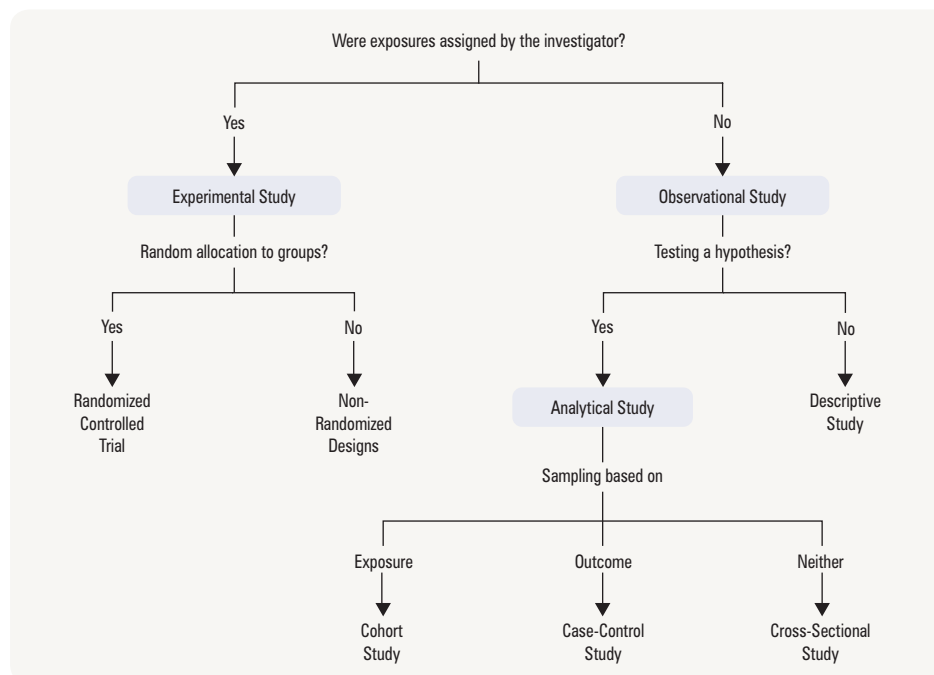


Figure 7. Quantitative study designs

Source: Adapted from <http://phprimer.afmc.ca>



## Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study subjects
- there are two main subtypes of observational studies: descriptive and analytic studies

### Descriptive Studies

- describe the events and rates of disease with respect to person, place and time and to estimate disease frequency and time trends
- first sets of studies and are used to generate an etiologic hypothesis, not test a hypothesis

### Analytic Studies

- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

**Table 6. Observational Study Designs**

Type of Study	Ecological	Cross-Sectional	Case-Control (Figure 8)	Cohort (Figure 9)
<b>Definition</b>	Units of analysis are populations or groups of people, rather than individuals	Assessment of individuals with respect to presence and absence of exposures and diseases at the same point in time	Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)	Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor
<b>Subjects</b>	Population (e.g. geographic areas)	Population (sample)	Two study sample populations are compared: cases and controls	One or more cohorts Cohort: group of people with common characteristics (e.g. year of birth) Divided into measured exposed vs. non-exposed groups
<b>Methods</b>	Accurate descriptions of the average exposure or risk of disease for a population	Collect information from each person at one particular time Tabulate the numbers in groups (e.g. by presence or absence of disease/factor of interest) Make 2 x 2 table and compare groups Estimate prevalence	Ask cases and controls about exposures Select all the cases of a specific disease during a specific time frame Representative of spectrum of clinical disease Select control(s) Represent the general population To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender) Association can be concluded between the risk factor and the disease (odds ratio) Estimate incidence	Subjects are followed for a specific period of time to determine development of disease in each exposure group Prospective: measuring from the exposure to the future outcomes – looking forward Retrospective: measuring from outcomes to possible risk factors or protective factors – looking back  Collect information on factors from all persons at the beginning of the study Tabulate the number of persons who develop the disease or other measured outcomes of morbidity Provides estimates of incidence, relative risk, attributable risk
<b>Advantages</b>	Quick, easy to do Uses readily available data Generates hypothesis	Determines association between variables Quick and uses limited resources Surveys with validated questions allows comparison between studies	Used when disease in population is rare (less than 10% of population) due to increased efficiency Less costly and time consuming	Shows an association between a factor and an outcome/several outcomes Stronger evidence for causation
<b>Disadvantages</b>	Poor generalizability to individual level (not direct assessment of causal relationship) Ecological fallacy: an incorrect inference about individuals in the population	Does not allow for assessment of temporal relationship or causation between variables Recall bias (see PH8)	Recall bias (see PH8) Confounding Selection bias for controls Only one outcome can be measured	By itself, cannot establish causation Confounding factors are common as the cohort self-selects the exposure, or unknown/unmeasured factors are associated with the measured exposure Cost and duration of time needed to follow cohort



An example of a descriptive study is one that explores the rates of AIDS by age, sex, geographic distribution, and over time.



### Formulating a Research Question

#### PICO

**P**atient Characteristics

**I**ntervention of Interest

**C**omparison Group or Control Group

**O**utcome that you are trying to prevent or achieve



An example of an ecological study would be one looking at the association between smoking rates and lung cancer rates in different countries.



An example of an ecological fallacy would be concluding that red wine drinking leads to lower risk of death from CVS disease after an ecological study shows that France has a higher rate of red wine consumption and a lower rate of death from CVS causes.



An example of a cross sectional study is one that examines the distribution of BMI by age in Ontario at a particular point in time.



An example of a famous case control study is by Sir Richard Doll who demonstrated the link between tobacco smoking exposure and lung cancer cases.



An example of a famous cohort study is the Framingham Heart Study, which assesses the long-term cardiovascular risks of diet, exercise, medications such as Aspirin®, etc.

## Experimental Study Designs

- not discussed here are non-randomized control trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible) and clinical trials (test treatments or laboratory tests in human subjects)

### 1. RANDOMIZED CONTROLLED TRIAL (RCT)

#### Definition

- subjects are assigned by random allocation to two or more groups, one of which is the control group, the other group(s) receive(s) an experimental intervention

#### Subjects

- individuals are separated into groups by a random process to ensure as much as possible equal distribution of known and unknown factors except for the experimental exposure (e.g. the treatment)

#### Methods

- random allocation of individuals into two or more treatment groups through a centralized concealed process
- method of assessment to reduce bias
  - single-blind:** subject does not know group assignment (intervention or placebo)
  - double-blind:** subject and observer both unaware of group assignment
  - triple-blind:** subject, observer, and analyst unaware of group assignment (rarely done)
- one group receives placebo or standard therapy
- one or more groups receive(s) the intervention(s) under study
- the outcome is measured and the groups are compared
- all other conditions are kept the same between groups

#### Advantages

- “gold standard” of studies, upon which the practice of EBM is founded
- provides the strongest evidence for effectiveness of intervention
- with sufficient sample size and appropriate randomization, threats to validity are minimized
- allows prospective assessment of the effects of intervention while minimizing bias

#### Disadvantages

- some exposures are not amenable to randomization (e.g. cannot randomize subjects to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
- difficult to randomly allocate groups (e.g. communities, neighbourhoods)
- difficult to study rare events, since RCTs would require extremely large sample sizes
- costly

## Other Study Designs

### 1. META-ANALYSIS

#### Definition

- combines the results of independent (studies identified through a systematic review) that address a common research hypothesis into one large study

#### Subjects

- combination of all the subjects used in original studies

#### Methods

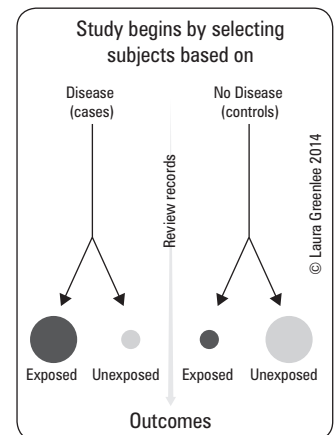
- selection of relevant studies from the published literature which meet quality criteria
- statistical models used to combine the results of each independent study
- provides a summary statistic of overall results as well as graphic representation of included studies

#### Advantages

- attempts to overcome the problem of reduced power due to small sample sizes of individual studies
- ability to control for inter-study variation

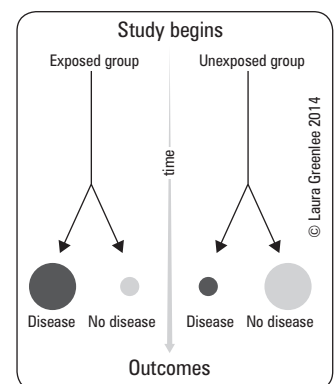
#### Disadvantages

- sources of bias may not be controlled for
- reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)
- the decision to include/reject a particular study is subjective



**Figure 8. Case-control study**

Adapted from <http://phprimer.afmc.ca>



**Figure 9. Cohort study**

Adapted from <http://phprimer.afmc.ca>



An example of an RCT is the SPARCL trial, which demonstrated intense lipid-lowering with atorvastatin reduces the risk of cerebro- and cardiovascular events in patients with and without carotid stenosis when compared to placebo.



An example of a meta-analysis is one that includes the full set of reported studies based on compiling and analyzing data from eligible RCTs, which compare the effects of ACE inhibitors, CCBs, and other antihypertensive agents on mortality and major cardiovascular events.

# Methods of Analysis

## Distributions

- distribution describes the probability of events
- normal (Gaussian) or non-normal (skewed, bimodal, etc.)
- characteristics of the normal distribution
  - mean = median = mode
  - 67% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - **mean:** sum of all observations divided by total number of variables
  - **median:** value at the 50th percentile, this is a better reflection of the central tendency for a skewed distribution
  - **mode:** most frequently observed value in a series
- measures of dispersion
  - **range:** the largest value minus the smallest value
  - **variance:** a measure of the spread of data
  - **standard deviation:** the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

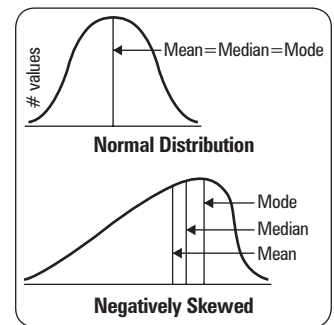


Figure 10. Distribution curves



### Example Calculation

Data set: 17, 14, 17, 10, 7

Mean =  $(17 + 14 + 17 + 10 + 7) \div 5 = 13$

Median (write the list in order, median is the number in the middle)  
= 7, 10, 14, 17, 17 = 14

Mode (number repeated more often)  
= 17

Range =  $17 - 7 = 10$

Variance =  $[(17 - 13)^2 + (14 - 13)^2 + (17 - 13)^2 + (10 - 13)^2 + (7 - 13)^2] \div 5 = 19.5$

Standard Deviation =  $\sqrt{\text{variance}} = \sqrt{19.5} = 4.42$



### Type I ( $\alpha$ ) Error

"There Is An Effect" where in reality there is none.

## Data Analysis

### Statistical Hypotheses

- **null ( $H_0$ )**
  - no relationship exists between the two stated variables (i.e. no association between the hypothesized exposure and the outcome)
- **alternative ( $H_1$ )**
  - a relationship does exist between the two stated variables

### Type I Error ( $\alpha$ Error)

- the null hypothesis is falsely rejected (e.g. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error, since a type I error can have larger clinical significance than a type II error

### Type II Error ( $\beta$ Error)

- the null hypothesis is falsely accepted (e.g. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- higher level of error is acceptable for most studies
- can also be used to calculate statistical power

### Power

- probability of correctly rejecting a null hypothesis when it is in fact false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
- power increases with an increase in sample size
- power =  $1 - \beta$ , and is therefore equal to the probability of a true positive result

### Statistical Significance

- the probability that the statistical association found between the variables is due to random chance alone (i.e. that there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently  $p=0.05$
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (i.e.  $p < 0.05$ )

### Clinical Significance

- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient compliance, and side effects in addition to statistical significance

### Trend

- an observed directional relationship that does not meet criteria for statistical significance and thus should be interpreted with caution

### Confidence Interval (CI)

- provides a range of values within which the true population result (e.g. the mean) lies
- frequently reported as 95% CI (e.g. one can be 95% certain that the true value is within this data range)
- bounded by the upper and lower confidence limits



A wider confidence interval implies more variance than a tighter confidence interval.

### Data

- information collected from a sample of a population
- there are 2 overall classes of data listed with examples:
  - **discrete**
    - ♦ categorical (e.g. gender, marital status)
    - ♦ ordinal (e.g. low, medium, high)
  - **continuous** (e.g. serum cholesterol, hemoglobin, age)

### Accuracy

- how closely a measurement approaches the true value

### Reliability

- how consistent a measurement is when performed by different observers under the same conditions or by the same observer under different conditions

### Validity

- extent to which a measurement approaches what it is designed to measure
- determined by the accuracy and reliability of a test

### Internal Validity

- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the precision and accuracy

### External Validity

- degree to which the results of the study can be generalized to other situations or populations

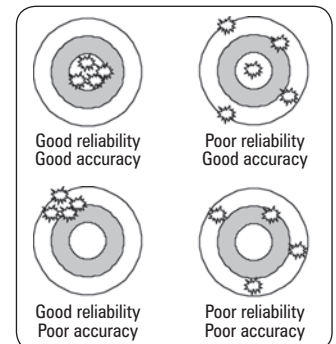


Figure 11. Accuracy vs. reliability

## Common Statistical Tests

Table 7. Statistical Tests

	Z-Test (known as t-test for samples <30)	Analysis of Variance (ANOVA)	Chi-square Test ( $\chi^2$ )	Linear Regression	Logistic Regression
What are you trying to show?	Compare the mean values of an outcome variable between two groups (e.g. difference in average BP between men and women)	Compare the mean values of an outcome variable between two or more groups (e.g. difference in average BP between persons in three towns)	Test the correspondence between a theoretical frequency distribution and an observed frequency distribution. (e.g. if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test determines if this variation is more than expected due to chance alone)	Looks at associations between two or more continuous variables (e.g. age and blood pressure)	Show how a change in one explanatory variable affects the status (e.g. ill vs. non-ill) of the outcome variable
What kind of data do you have in your study?	Data on two groups	Mean of groups (one or more) Overall mean of an entire sample	Data on two or more populations and two or more outcome measures	Data on at least one population	Data on at least one population
What kind of variables do you measure?					
Dependent variable	Continuous data	Continuous data	Categorical (2 or more)	Continuous	Categorical (discrete outcomes usually dichotomous)
Independent variable	Categorical (2 only)	Categorical (2 or more)	Categorical (2 or more)	Continuous	Continuous/categorical
Assumptions		"Normal" distribution	None	Dependent variable has "normal" distribution Linear relationship between variables	None

## Causation

### Criteria for Causation (Sir Bradford Hill)

1. **strength of association:** the frequency with which the factor is found in the disease and the frequency with which it occurs in the absence of disease
2. **consistency:** is it the same outcome with different populations or study design?
3. **specificity:** is the association particular to your intervention and measured outcome?
4. **temporal relationship:** did the exposure occur before the onset of the disease?
5. **biological gradient:** finding a quantitative relationship between the factor and the frequency (e.g. dose response relationship)
6. **biological plausibility:** does the association/causation make biological sense?
7. **coherence:** can the relationship be explained/accounted for based on what we know about the laws of science, logic, etc.?
8. **experimental evidence:** experiment that investigates what happens when the suspected offending agent is removed (e.g. is there improvement?)
9. **analogy:** do other established associations provide a model for this type of the relationship?

**Note:** not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes 'experimental evidence' as superior to other criteria for experimental causation review. However many causation questions in health cannot be answered with experimental methods.

- visit <http://phprimer.afmc.ca> and refer to Table 5.4: Criteria for inferring a causal relationship from the AFMC Primer on Population Health



#### Beware:

##### Correlation ≠ Causation

e.g. There is evidence of a direct correlation between the amount of ice cream sold and the amount of deaths in swimming pools. Of course, ice cream does not cause drowning, rather, they both increase in the summer.



#### Criteria for Causation

##### ACCESS PTB

Analogy  
Consistency  
Coherence  
Experimental evidence  
Strength of association  
Specificity  
Plausibility  
Temporal relationship  
Biological gradient



#### Validity

- The degree to which the outcome observed in the study can be attributed to the intervention

#### 5 Questions About the Validity of Primary Studies

- Were the patients randomized?
- Was the follow-up of patients sufficiently long and complete?
- Were all patients analyzed in the groups to which they were randomized?
- Were the groups treated equally except for the intervention?
- Were the patients and clinicians kept blind to treatment?

#### Other Questions to Consider

- Were the groups similar (i.e. demographics, prognostic factors) at the start of the trial?
- Were the appropriate and valid exposure and outcome measures obtained?
- Were outcome assessors aware of group allocation?
- Was contamination reported?
- Were ethical issues continuously upheld?



#### Analysis

##### Per-Protocol Analysis (PP)

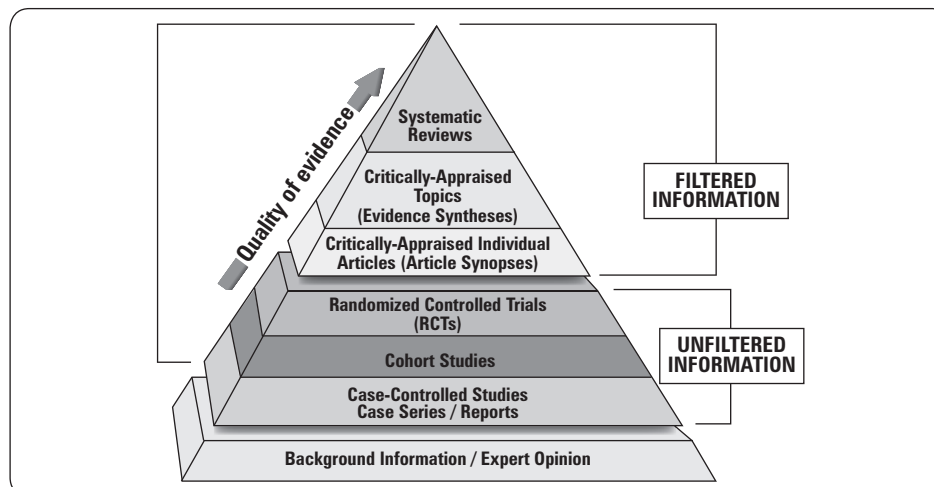
Strategy of analysis in which only patients who complete the entire study are counted towards the results.

##### Intention-to-Treat Analysis (ITT)

When groups are analyzed exactly as they existed upon randomization (i.e. using data from all patients, including those who did not complete the study).

## Assessing Evidence

- critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision



**Figure 12. Pyramid of pre-appraised evidence**

© Copyright 2006. Trustees of Dartmouth College & Yale University. All rights reserved. Produced by Glover J., Izzo D., Odatto K. and Wang L.

### A. Are the results of the study valid?

- see below for classifications of evidence that has already been assessed; see sidebar for assessing primary studies

### B. What are the results?

- what was the impact of the treatment effect?
- how precise was the estimate of treatment effect?
- what were the confidence intervals and power of the study?

### C. Will the results help me in caring for my patients?

- are the results clinically significant?
- can I apply the results to my patient population?
- were all clinically important outcomes considered?
- are the likely treatment benefits worth the potential harm and costs?



#### Canadian Task Force on Preventive Health Care Grading of Health Promotion Actions

- A:** *Good evidence to recommend the preventive health measure*
- B:** *Fair evidence to recommend the preventive health measure*
- C:** *Existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making*
- D:** *Fair evidence to recommend against the preventive health measure*
- E:** *Good evidence to recommend against the preventive health measure*
- I:** *Insufficient evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making*

Source: Canadian Task Force on Representative Health Care. Canadian task force on preventive new grades for recommendations. *CMAJ* 2003;169:207-208

#### Levels of Evidence: Classifications Cited in Guidelines/Consensus Statements

Level I evidence: based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results

Level II evidence: based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results

Level III evidence: based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies

Level IV evidence: based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines

Level V evidence: opinions of the individuals who have written/reviewed the guidelines (i.e. Level IV evidence), based on experience/knowledge of literature/peer discussion

Notes: These 5 levels of evidence are not direct evaluations of evidence quality or credibility; they reflect the nature of the evidence. While RCTs tend to be most credible (with <III), level III evidence gains credibility when multiple studies from different locations and/or time periods report consistent findings. Level IV and V evidence reflects decision-making that is necessary but in the absence of published evidence.

**Figure 13. Levels of evidence classifications**

Note: this is only one method of classifying evidence. Various systems exist, but operate within the same premise that certain types of evidence carry more weight than others

## Health Services Research



### Continuous Quality Improvement (CQI)

#### Quality Improvement

- method of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to be the cause of variation in quality, as opposed to individuals
- taking measures to increase efficiency of action with the purpose of achieving optimal quality

#### Quality Assurance

- management system to assure the quality of health care provided by workers and received by patients
- constantly aims to improve standards and the frequency of attaining those standards
- **five-stage process of quality assurance**
  - establishment of functional goals
  - implementation of procedures to achieve those goals
  - regular assessment of performance relative to the goals
  - proposal of solutions to close the gap between performance and goals
  - documentation and reporting of this assessment activity

#### Quality Control

- method of maintaining standards by reviewing the quality of all factors involved in the process

#### Continuous Quality Improvement

- management approach to improve and maintain quality via continuous assessment of potential defects, followed by action to improve process, avoid decrease in quality or correcting process in early stages
- continuous feed-forward process

#### Quality Management

- encompasses quality assurance, quality control and quality improvement to achieve consistent quality

#### Total Quality Management

- management philosophy for improving quality while controlling costs
- focusing on the system rather than the individual, to ensure decisions are made to support quality and remove barriers to quality inherent in bureaucratic, hierarchical systems

#### Audit

- process of systematic examination of a quality system carried out by internal or external quality auditors
- to determine whether quality processes and results comply with goals, and whether processes have been implemented effectively

#### Systems Analyses Tools

1. **5 Whys:** brainstorming to simplify the process of change; continue asking 'why' until the root of the problem is discovered
2. **Ishikawa Diagrams (aka Fishbone Diagrams):** identify generic categories of problems that have an overall contribution on the effect (see Figure 13)



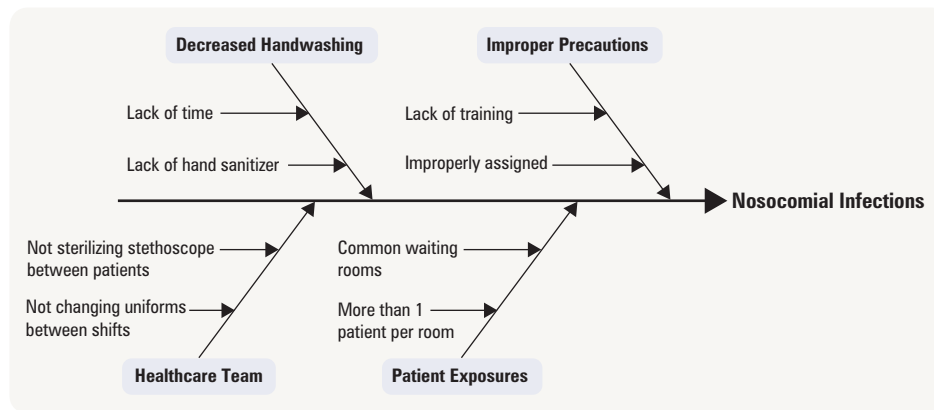


Figure 14. Ishikawa diagram

3. **Defect check sheets:** consider all defects and tally up the number of times the defect occurs

4. **Pareto Chart:** x vs. y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis

- purpose is to highlight most important among large set of factors contributing to defects/poor quality

### Precede-Proceed Model

- tool for designing, implementing, and evaluating health interventions/programs

Table 8. Precede-Proceed Model

PRECEDE Phase	PROCEED Phase
Phase 1 – Identify the ultimate desired result	Phase 5 – Implementation (design and conduct the intervention)
Phase 2 – Identify and set priorities among health issues and their behavioural and environmental determinants	Phase 6 – Process Evaluation (determine if the program is implemented as planned)
Phase 3 – Identify the predisposing, enabling, and reinforcing factors that affect the behaviours and environmental determinants	Phase 7 – Impact Evaluation (measure intermediate objectives – predisposing, enabling, and reinforcing factors)
Phase 4 – Identify the administrative and policy factors that influence what can be implemented	Phase 8 – Outcome Evaluation (measure desired result)

## Cost Analysis

### Cost Benefit Analysis

- a process of, either explicitly or implicitly, weighing the total expected costs against the total expected benefits of one or more actions in order to choose the best or most profitable option
- all costs are adjusted for the time value of money, so that costs that may change over time are expressed on a common basis in terms of their present value

### Cost Effectiveness Analysis (CEA)

- a comparison of the relative expenditure (costs) and outcomes (effects) of two or more courses of action
- cost effectiveness analysis is often used where a full cost benefit analysis is inappropriate
- a CEA is commonly expressed in terms of a ratio: the denominator is a gain in health from a measure (e.g. years of life, premature births averted, sight-years gained) and the numerator is the cost of the health gain
- the most commonly used outcome measure is quality-adjusted life years (QALY)

## Outbreak of Infectious Diseases



### Definitions

#### Outbreak

- occurrence of new cases clearly in excess of the baseline frequency of the disease in a defined community or population over a given period of time
- synonymous with epidemic, although generally considered to be an epidemic that is localized, has an acute onset, or is relatively short in duration

**Epidemic**

- any disease, infectious or chronic, occurring at a greater frequency than usually expected in a defined community or institutional population over a given time period (i.e. excessive rate of disease)

**Endemic**

- constant presence of disease or infectious agent in a given geographic area or population subgroup (i.e. usual rate of disease)

**Pandemic**

- epidemic over a wide area, crossing international boundaries, and affecting a large number of people

**Attack Rate**

- cumulative incidence of infection within a defined group observed during a specific period of time in an epidemic
- calculated by dividing the total number of people who develop clinical disease by the population at risk, usually expressed as a percentage

**Secondary Attack Rate**

- number of cases among contacts occurring within the incubation period following exposure to the primary case, in relation to the total exposed contacts
- infectiousness reflects the ease of disease transmission and is usually measured by the secondary attack rate

**Pathogenicity Rate**

- power of an organism to produce clinical disease in those that are affected

**Virulence**

- severity of the disease produced by the organism in a given host
- expressed as the ratio of the number of cases of severe and fatal infection to the total number of clinically affected

**Case-Fatality Rate**

- proportion of individuals contracting a disease who die as a result of that disease
- most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths
- must be clearly differentiated from the mortality rate

**Mortality Rate/Crude Death Rate**

- estimation of the portion of the population that dies during a specified period from all causes of death

**All-Cause Mortality Rate by Age Group**

- estimation of the portion of the population in a given age group that dies during a specified period from all causes of death for that age group

**Morbidity Rate**

- estimation of the portion of the population that suffers illness or ill health during a specified period

**Infection Control Precautions**  
(see [Infectious Diseases](#), ID6)**Contact** (impetigo, chicken pox, warts)

- Wash hands
- Gloves
- Gown
- Wipe equipment after use

**Airborne** (TB)

- Contact precautions PLUS
- N95 mask (fit tested)
- Negative pressure room

**Droplet** (influenza, mumps, pneumonia)

- Contact precautions PLUS
- Goggles/face shield
- Surgical mask

Source: Public Health Ontario. <http://www.oahpp.ca/resources/documents/pidac/2011-01%20BP%20Infection%20Prevention%20Control.pdf>  
<http://www.oahpp.ca/resources/documents/pidac/Routine%20Practices%20and%20Additional%20Precautions.pdf>

## Steps to Control an Outbreak

**1. Define the Problem**

- is it an outbreak?

**2. Appraise Existing Data and Institute a Surveillance System**

- case definition:** formulated from the most common symptoms or signs; definition includes the likely date of onset of illness of the first case (e.g. any person with onset of fever higher than 38.5°C and cough within past 28 d)
- active surveillance:** identify those who may have been exposed to the infectious agent and who fit the case definition through active efforts, including:

**3. Formulate Hypotheses and Implement Initial Control Measures**

- track outbreak evolution to develop hypotheses about potential source and populations at risk
- case management depends on symptoms, suspected agent, population at risk, and location
- population management requires public health services in the community and infection control teams in hospitals to disseminate information about
  - risk reduction
  - personal preventative measures (e.g. post-exposure prophylaxis)
  - decreasing risk of propagation (e.g. quarantine)

#### 4. Test the Hypothesis through Analysis of Surveillance Data or Special Studies

- analyze outbreak surveillance data
- generate epidemic curves
  - usually a frequency histogram, with the number of cases plotted on the vertical axis and dates or times of onset along the horizontal axis
  - curve can indicate whether the epidemic (outbreak) has a common source or whether it is propagated
  - **point source epidemic:** exposure is brief and essentially simultaneous (see Figure 15a)
  - extended source epidemic: exposure lasts for a period of days to weeks and may be continuous (no irregular peaks, see Figure 15b) or intermittent (irregularly spaced peaks)
  - **propagated epidemic:** begins with only a few exposed persons but is maintained by person-to-person transmission (e.g. measles/influenza); epidemic curve shows a series of peaks (see Figure 15c)
- use epidemic curves, cross-sectional studies, and/or case-control studies to evaluate hypotheses about cause of outbreak

#### 5. Draw Conclusions and Re-Adjust Hypothesis and Control Measures

- establish cause of outbreak with further epidemiologic investigation and revise initial control measures accordingly

#### 6. Plan for Long-Term Prevention and Control

- implement prevention measures to avoid similar future incidents
  - strengthen resistance of hosts (e.g. immunization)
  - interrupt modes of transmission in environment (e.g. improvements in food processing)
- communicate outbreak prevention and control strategies to the public

For specific examples, see "Communicable Diseases" section in: Shah CP. Public Health and Preventive Medicine in Canada. Toronto: Elsevier, 5th edition, 2003

Figure 15. Epidemic curves

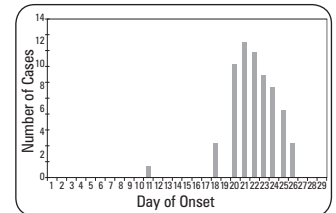


Figure 15a. Point source epidemic curve

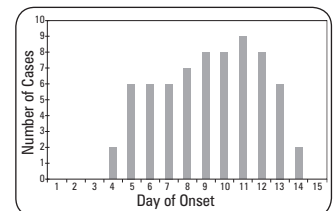


Figure 15b. Extended continuous source epidemic curve

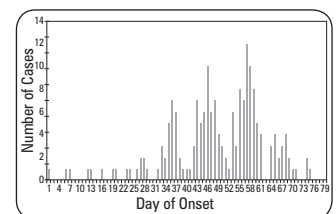


Figure 15c. Propagated source epidemic curve

## Environmental Health



### Definition

- study of conditions in the natural and human-made environment that influence human health and well-being
- environmental exposures
  - four main reservoirs: air, food, water, and soil
  - three main routes: inhalation, ingestion, or absorption (skin)
  - usually divided into two main settings:
    - ♦ workplace (including schools): may see high level exposure in healthy individuals (see *Occupational Health*, PH23)
    - ♦ non-workplace: generally low level but chronic exposure; population at risk includes extremes of age, developing fetuses, and ill or immunocompromised individuals
- health impacts of the environment also include factors such as urban planning and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths are neighbourhood features that can facilitate more active lifestyles among residents)

## Environmental Health Jurisdiction

Table 9. Environmental Health Jurisdiction

<b>Public Health Unit</b>	Enforcement of water and food safety regulations (including restaurant food safety) Sanitation Assessment of local environmental risks Monitoring and follow-up of reportable diseases
<b>Municipal Government</b>	Waste disposal Recycling Water and sewage treatment/collection/distribution
<b>Provincial and Territorial Government</b>	Water and air quality standards Industrial emission regulation Toxic waste disposal
<b>Federal Government</b>	Designating and regulating toxic substances Regulating food products (e.g. Health Canada) Setting policy for pollutants that can travel across provincial boundaries
<b>International</b>	Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change, International Joint Commission)



### Active Surveillance

Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection).

### Passive Surveillance

A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered).

## Risk Assessment

### Hazard Identification

- what is the hazard involved?
- assess potential hazards by taking an environmental health history

### Risk Characterization

- is the identified agent likely to elicit the patient's current symptoms?
- review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. some agents only become dangerous at threshold levels)

### Exposure Assessment

- is the patient's exposure to the environmental agent sufficient to have caused the current symptoms?
- quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard



#### Taking an Environmental Health History

CH<sub>2</sub>OPD<sub>2</sub>  
Community  
Home  
Hobbies  
Occupation  
Personal habits  
Diet  
Drugs

## Air

### Physical Contaminants

- sound waves
  - ionizing radiation
  - radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with a small proportion of lung cancers
- ultraviolet radiation is increasing due to ozone layer destruction and increases risk of skin cancer
  - non-ionizing radiation
  - visible light, infrared, microwave



#### Effects of Ionizing Radiation

$\alpha$ -particles are larger and damage the skin and bronchial lining (airway irritation).

$\beta$ -particles are smaller and cause deeper damage (alveoli).

### Chemical Contaminants

- ground-level ozone
  - main component of smog with levels increasing in major cities
  - worsens asthma, irritates upper airway
- carbon monoxide (fossil fuel related, common byproduct of combustion)
  - aggravates cardiac disease at low levels
  - headache, nausea, dizziness at moderate levels
  - fatal at high levels
- sulphur dioxide (fossil fuel related), nitrogen oxides
  - contribute to acid rain
  - exacerbate breathing difficulties
- organic compounds (e.g. benzene, methylene chloride, tetrachloroethylene)
  - variety of health effects at high levels (e.g. benzene is a known carcinogen)
  - tend to be fat-soluble, easily absorbed through skin and difficult to excrete
- heavy metals (e.g. nickel, cadmium, chromium)
  - present in industrial emissions
  - variety of health effects: upper airway disease, asthma, decreased lung function
- second hand tobacco smoke
  - respiratory problems, increase risk of lung cancer



#### BPA, the Toxin Concern of 2009

Bisphenol A (BPA) is a chemical compound found in some hard, clear, lightweight plastics and resins. According to the NIH, animal studies suggest that ingested BPA may imitate estrogen and other hormones. In October 2008, Canada became the first country in the world to ban the import and sale of polycarbonate baby bottles containing BPA, stating that although exposure levels are below levels that cause negative effects, current safety margins need to be higher. The US FDA does not consider normal exposure to BPA to be a hazard, however the NIH has some concern that fetuses, infants, and children exposed to BPA may be at increased risk for early-onset puberty, prostate, and breast cancer.

### Biological Contaminants

- particulates
  - associated with decreased lung function, asthma, upper airway irritation
- moulds thrive in moist areas; 10-15% of the population allergic
- bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. *Legionella*)
- dust mites (year-round) and pollens (seasonal) can trigger upper and lower-airway symptoms

### Climate Change

- anthropogenic greenhouse gas emissions (e.g. carbon dioxide, methane) leading to adverse changes in the global environment
  - increased extreme weather conditions (e.g. floods, hurricanes, heat waves)
  - increased distribution of disease vectors (e.g. mosquitoes and malaria)
  - increased malnutrition from crop failures
  - increased diarrheal diseases

## Water

### Biological Contaminants

- mostly due to human and animal waste
- Aboriginal Canadians, rural Canadians at higher risk
- bacteria: *Escherichia coli* (e.g. Walkerton, ON), *Salmonella*, *Pseudomonas*, *Shigella*
- protozoa: *Giardia*, *Cryptosporidium* (e.g. North Battleford, SK)

### Chemical/Industrial Contaminants

- chlorination by-products (e.g. chloroform can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides, and other industrial waste products can be present in groundwater
- fluoride at high levels (greater than that of municipal fluoridation) can cause skeletal fluorosis

## Soil

- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, direct discharge of industrial wastes, lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- health effects:
  - infants and toddlers at highest risk of exposure due to hand-mouth behaviours
  - dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue
- biological contamination: tetanus, *Pseudomonas*

## Food

Table 10. Comparison of Select Biological Contaminants of Food and Effects on Human Health

	Source	Effects
<i>Salmonella</i>	Raw eggs, poultry, meat	GI symptoms
<i>Campylobacter</i>	Raw poultry, raw milk	Joint pain, GI symptoms
<i>Escherichia coli</i>	Various including meat, sprouts Primarily undercooked hamburger meat	Watery or bloody diarrhea Hemolytic uremic syndrome (esp. children)
<i>Listeria monocytogenes</i>	Unpasteurized cheeses, prepared salads, cold cuts	Listeriosis: nausea, vomiting, fever, headache, rarely meningitis or encephalitis
<i>Clostridium botulinum</i>	Unpasteurized honey, canned foods	Dizziness, weakness, respiratory failure, GI symptoms: thirst, nausea, constipation
<b>Prion (BSE)</b>	Beef and beef products	Creutzfeldt-Jakob disease

BSE = bovine spongiform encephalopathy

- other biological food contaminants include:
  - viruses
  - mould toxins (e.g. aflatoxin → liver cancer)
  - parasites (e.g. *Toxoplasmosis*, tapeworm)
  - paralytic and shellfish poisoning (rare)
  - genetically modified organisms (GMO) – controversial with respect to health and environmental risk/benefits

### Chemical Contaminants

many persistent organic pollutants are fat-soluble and undergo bioamplification

- drugs (antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrites highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
- pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects
  - debate over risks of DDT vs. risks of malaria in malaria-endemic countries



### To Fluoridate or Not

At the recommended concentration of 0.8-1.0 mg/L, fluoride reduces cavities by 18-40%, and there is little risk of fluorosis unless other exposures (e.g. toothpaste, rinses, mouthwash, etc.) are swallowed. Opposition raises concerns that the intake is not easily controlled, and that children, and others may be more susceptible to health problems. However, public health experts strongly support fluoridation as an effective measure to prevent dental caries at the community level and reduce dental health inequities.



### The Walkerton Tragedy

In May 2000, the drinking water system in the town of Walkerton, ON, became contaminated with *Escherichia coli* O157:H7 and *Campylobacter jejuni*. Over 2,300 individuals became ill; 27 people developed hemolytic uremic syndrome and 7 individuals died in the outbreak.

Source: Ministry of the Attorney General. Report of the Walkerton inquiry. Ontario, 2002.



### Honey and Botulism

Although exceedingly rare, infant botulism has been documented as a form of food poisoning from *C. botulinum* found in honey. When an infant swallows spores of this bacterium, they grow and produce a toxin in the baby's intestine. By the time an infant is 1, its gut has a healthy colony of "good" bacteria that prevents this from occurring.



### Organic Foods

- Foods designated as "organic" in Canada must conform to the Organic Products Regulations enforced by the Canadian Food Inspection Agency
- Organic foods are not free of synthetic pesticide residues but typically contain smaller amounts compared to conventionally grown foods
- Currently, there has not been strong evidence to suggest that eating organic foods is safer or more nutritious compared to eating conventionally grown food

Source: Health Canada. Pesticides and food, 2011. UpToDate. Organic foods and children, 2009.

- polychlorinated biphenyls (PCBs)
  - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
- dioxins and furans
  - levels highest in fish and marine mammals, also present in breast milk
  - can cause immunosuppression, liver disease, respiratory disease

## Heavy Metal Toxicity

### Mechanism

- after exposure, superabundant metals bind to proteins, alter their enzymatic activity, and lead to diffuse disease manifestations

### Predisposing Factors in At-Risk Groups

- children: hand-to-mouth, incomplete blood brain barrier
- pregnant women and developing fetus: heavy metals cross placenta; mothers release heavy metal stores at times of calcium stress
- adults: occupation, hobbies, environment (home, country)

### Etiology

- iatrogenic (e.g. gold treatment for rheumatoid arthritis, lithium treatment for bipolar affective disorder)
- inhalation (e.g. zinc oxide, lead gasoline fumes)
- ingestion (e.g. lead paint, mercury in fish, folk remedies)
- industry (e.g. methyl mercury industrial spill caused Minamata disease)

### Treatment

- generalized workup: symptoms are usually wide-ranging and non-specific
- chelation therapy (e.g. dimercaprol)

## Occupational Health

- occupational health is the maintenance and promotion of health in the work environment
- occupational health services include physicians, nurses, engineers, ergonomists, safety officers, physicists, technicians and others
- services encompass health promotion and protection (primary prevention), disease prevention (secondary prevention), and treatment and rehabilitation (tertiary prevention)
- general bias towards reporting occupational injuries versus occupational disease, as occupational disease is harder to identify



#### Occupational Health Statistics

- 939 workplace fatalities and 260,284 lost-time injuries in Canada in 2009
- 5703 fatal work injuries in the United States in 2006; rate = 3.9/100,000 workers

## Workplace Health Promotion and Protection

- take action in the workplace so the worker is protected from injury or illness
  - identifying workplace hazards [e.g. through material safety data sheets (MSDS)]
  - assessing risk
  - reducing exposure
    - ♦ **source:** substituting a less toxic chemical
    - ♦ **path:** enclosing a source of noise in a sound-proof room
    - ♦ **worker:** personal protection equipment (e.g. reflective vests, helmets)
    - ♦ **worker education:** emergency protocols, material safety education
    - ♦ **rotation of workers:** decrease exposure for each worker but more workers exposed



#### Reducing Exposure in the Workplace

- Engineering controls – most preferred
- Administrative/work practices
- Personal protective equipment – least preferred due to adherence challenges

## Workplace Disease Prevention

- monitor workers' health to prevent the development of disease
  - periodic examinations to facilitate pre-symptomatic diagnosis (e.g. screening for lead exposure); substance misuse screening where performance impairment is suspected

## Workplace Treatment and Rehabilitation

- treat injury or illness with safe return to the workplace
- may require rehabilitation, retraining, change in job duties, and/or workers' compensation





### Ontario's *Workplace Safety and Insurance Act* (Each province will have their own similar legislation)

- Establishes Workplace Safety and Insurance Board (WSIB), an autonomous government agency that oversees workplace safety training and administers insurance for workers and employers
- WSIB decides benefits for workers, which may include reimbursement for
  - Loss of earned income
  - Non-economic loss (e.g. physical, functional, or psychological loss extending beyond the workplace)
  - Loss of retirement income
  - Health care expenses (e.g. first-aid, medical treatment)
  - Survivor benefits (e.g. dependents and spouses can receive benefits)
- Employers pay for costs (e.g. no government funding)
- No-fault insurance (e.g. worker has no right to sue the employer) in return for guaranteed compensation for accepted claims
- Negligence is not considered a factor
- Physicians are required to provide the WSIB with information about a worker's health without a medical waiver once a claim is made

For more info: <http://www.wsib.on.ca/en/community/WSIB>



### Taking an Occupational Health Hx:

#### WHACS

**W**hat do you do?

**H**ow do you do it?

**A**re you concerned about any particular exposures on or off the job?

**C**o-workers or others with similar problems?

**S**atisfied with your job?

*J Occup Environ Med 1998; 40:680-4*

## Workplace Legislation

- universal across Canada for corporate responsibility in the workplace: due diligence, application of Workplace Hazardous Materials Information System (WHMIS), existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally regulated industries (e.g. airports, banks, highway transport) under the *Canada Labour Code*
- Ontario's *Occupational Health and Safety Act*
  - sets out rights of workers and duties of employers, procedures for dealing with workplace hazards, and law enforcement
  - workers have the right to
    - ♦ participate (e.g. have representatives on joint health and safety committees)
    - ♦ know (e.g. be trained and have information about workplace hazards)
    - ♦ refuse work (e.g. workers can decline tasks they feel are overly dangerous)
    - ♦ stop work (e.g. 'certified' workers can halt work they feel is dangerous to other workers)
  - employers must take precautions to protect the health and safety of employees and investigate concerns
  - enforced by Ministry of Labour via inspectors
- *Health Protection and Promotion Act* (HPPA) (Ontario)
  - Medical Officer of Health has right to investigate and manage health hazards where workplace exposures may impact non-workers (e.g. community members living close to the work site)

## Taking an Occupational Health History

- current and previous job duties
- exposures
  - identification: screen for chemical, metal, dust, biologic, psychologic and physical hazards; review relevant workplace material safety data sheets (MSDS)
  - assessment: duration, concentration, route, exposure controls (e.g. ventilation, personal protective equipment)
- temporal relationship: changes in symptoms in relationship to work environment
- presence of similar symptoms in co-workers
- non-work exposures: home, neighbourhood, hobbies

## Occupational Hazards

**Table 11. Occupational Hazards**

Physical	Chemical	Biological	Psychosocial
<ul style="list-style-type: none"> <li>• Trauma (fractures, lacerations)</li> <li>• Noise (hearing loss)</li> <li>• Temperature (heat cramps, heat exhaustion, heat stroke)</li> <li>• Air pressure (barotrauma, decompression sickness)</li> <li>• Ergonomic               <ul style="list-style-type: none"> <li>• Repetitive use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment</li> <li>• Tenosynovitis, bursitis, carpal tunnel syndrome</li> </ul> </li> <li>• Radiation               <ul style="list-style-type: none"> <li>• Non-ionizing: visible light, infrared</li> <li>• Ionizing: UV, x-rays, γ rays</li> </ul> </li> <li>• Electricity</li> </ul>	<ul style="list-style-type: none"> <li>• Organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride)</li> <li>• Mineral dusts (e.g. silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis)</li> <li>• Heavy metals (e.g. nickel, cadmium, mercury, lead)               <ul style="list-style-type: none"> <li>• Lead is ubiquitous and can cause severe disability</li> </ul> </li> <li>• Gases (e.g. halogen gases, sulphur dioxide, carbon monoxide, nitrogen oxides)</li> <li>• Second hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage)               <ul style="list-style-type: none"> <li>• Exposure restricted in most municipal, provincial, and federal jurisdictions</li> </ul> </li> <li>• Skin diseases (major portion of compensations, e.g. contact dermatitis, occupational acne, pigmentation disorders)</li> </ul>	<ul style="list-style-type: none"> <li>• Exposure to bacteria, viruses, fungi, protozoa, Rickettsia</li> <li>• Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</li> <li>• Consider exposure to disease in endemic countries, travelers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. SARS, TB)</li> </ul>	<ul style="list-style-type: none"> <li>• Workload, responsibility, fear of job loss, geographical isolation, shift work, harassment (sexual/non-sexual)</li> <li>• Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</li> </ul>

## Appendix – Reportable Diseases

As an essential part of the health system, physicians in Canada are required by law to report certain diseases to public health for the following reasons:

1. to control the outbreak
  - if the disease presents an outbreak threat (e.g. measles, *Salmonella*, respiratory diseases in institutions)
2. to prevent spread
  - if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa Fever)
3. for surveillance
  - if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment and/or partner notification (e.g. gonorrhea, TB)

Physicians should also report unlisted diseases that appear in clusters.

The following list is based on the reportable diseases in Ontario for 2011.  
(Each province will have their own similar legislation)

Source: Health Protection and Promotion Act, O. Reg. 559/91, amended to O. Reg.49/07.

Acquired Immunodeficiency Syndrome (AIDS)	<i>Haemophilus influenzae b</i> disease, invasive	Rabies
Amebiasis	Hantavirus pulmonary syndrome	Respiratory infection outbreaks in institutions
Anthrax	Hemorrhagic fevers, including:	Rubella
	i. Ebola virus disease	Rubella, congenital syndrome
Botulism	ii. Marburg virus disease	
Brucellosis	iii. Other viral causes	
	Hepatitis, viral:	Salmonellosis
Campylobacter enteritis	i. Hepatitis A	Severe Acute Respiratory Syndrome (SARS)
Chancroid	ii. Hepatitis B	Shigellosis
Chickenpox (Varicella)	iii. Hepatitis C	Smallpox
<i>Chlamydia trachomatis</i> infections	iv. Hepatitis D (Delta hepatitis)	Streptococcal infections, Group A invasive
Cholera	Herpes, neonatal	Streptococcal infections, Group B neonatal
<i>Clostridium difficile</i> associated disease (CDAD) outbreaks in public hospitals	Human Immunodeficiency Virus (HIV)	<i>Streptococcus pneumoniae</i> , invasive
Cryptosporidiosis	Influenza	syphilis
Cyclosporiasis		
Cytomegalovirus infection, congenital	Lassa Fever	
	Legionellosis	Tetanus
Diphtheria	Leprosy	Transmissible spongiform encephalopathy, including:
	Listeriosis	i. Creutzfeldt-Jakob disease, all types
Encephalitis, including:	Lyme Disease	ii. Gerstmann-Sträussler-Scheinker syndrome
i. Primary, viral		iii. Fatal familial insomnia
ii. Post-infectious	Malaria	iv. Kuru
iii. Vaccine-related	Measles	Trichinosis
iv. Subacute sclerosing panencephalitis	Meningitis, acute:	Tuberculosis
v. Unspecified	i. Bacterial	Tularemia
	ii. Viral	Typhoid Fever
Food poisoning, all causes	iii. Other	
	Meningococcal disease, invasive	
Gastroenteritis, institutional outbreaks	Mumps	
Giardiasis, except asymptomatic cases		Verotoxin-producing <i>E. coli</i> infection
Gonorrhea	Ophthalmia neonatorum	indicator conditions, including Hemolytic Uremic Syndrome (HUS)
	Paratyphoid fever	
	Pertussis (whooping cough)	West Nile Virus illness, including:
	Plague	i. West Nile fever
	Poliomyelitis, acute	ii. West Nile neurological manifestations
	Psittacosis/Ornithosis	
	Q Fever	Yellow Fever
		Yersiniosis

## References

### Journals

- Bradford-Hill A. The environment and disease: association or causation? *Proc Royal Soc Med* 1965;58:295-300.
- Braveman PA. Monitoring equity in health and health care: a conceptual framework. *J Health Popul Nutr* 2003;21:181-92.
- Kass NE. An ethics framework for public health. *Am J Public Health* 2001;91:1776-1782.
- McCurdy SA, Morrin LA, Memmott MM. Occupational history collection by third-year medical students during internal medicine and surgery inpatient clerkships. *J Occup Environ Med* 1998;40:680-684.

### Government Resources

- Hamilton N, Bhatti T. Integrated model of population health and health promotion. Ottawa: Health Promotion and Programs, 1996.
- Canadian Public Health Association and WHO. Ottawa charter for health promotion. Ottawa: Health and Welfare Canada, 1986.
- Health Canada. Health and environment: partners for life. Ottawa: Minister of Public Works and Government Services Canada, 1997.
- Health Protection and Promotion Act, R.S.O. 1990, c. H.7.
- Health Protection and Promotion Act, R.S.O. 1990., c.H.7; O. Reg. 559/91, amended to O. Reg. 49/07.
- Ministry of the Attorney General. Report of the Walkerton inquiry, 2002.

### Textbooks

- Associated Faculties of Medicine of Canada (AFMC). Primer on public health (internet). AFMC, 2011. Virtual textbook available at: <http://phprimer.afmc.ca>.
- Hennekens C, Buring J. Epidemiology in medicine. Philadelphia: Lippincott, Williams & Wilkins, 1987.
- Hulley SB, Cummings SR. Designing clinical research: an epidemiologic approach. Baltimore: Williams & Wilkins, 1988.
- Kelsey JL, et al. Methods in observational epidemiology, 2nd ed. Oxford University Press, 1996.
- Last JM. A Dictionary of epidemiology, 4th ed. Oxford University Press, 2001.
- Sackett DL, Strauss SE, Richardson WS, Rosenberg W and Haynes RB. Evidence-based medicine: how to practice and teach EBM. 2nd ed. Toronto: Churchill, Livingstone, 2002.
- Shah CP. Public health and preventive medicine in Canada, 5th ed. Toronto: Elsevier Canada, 2003.

### Websites

- AFMC Primer on Population Health. Available from: <http://phprimer.afmc.ca/>.
- Association of Workers' Compensation Boards of Canada. Available from: <http://www.awcbc.org>.
- Bureau of Labor Statistics. Available from: <http://www.bls.gov>.
- Canada's National Occupational Health and Safety. Available from: <http://www.canoshweb.org>.
- Canadian Centre for Occupational Health and Safety. Available from: <http://www.ccohs.ca>.
- Canadian Food Inspection Agency. Available from: <http://www.inspection.gc.ca>.
- Canadian Institute for Health Information. Available from: <http://www.cihi.ca>.
- Canadian Medical Association. Available from: <http://www.cma.ca>.
- Canadian Public Health Association. Available from: <http://www.cpha.ca>.
- Canadian Society for International Health. Available from: <http://www.csih.org>.
- Canadian Task Force on Preventative Health Care. Available from: <http://www.canadiantaskforce.ca>.
- Center for Disease Control and Prevention. Available from: <http://www.cdc.gov>.
- Health Canada. Available from: <http://www.hc-sc.gc.ca>.
- Institute for Population and Public Health, Canadian Institutes for Health Research. Available from: <http://www.cihr-irsc.gc.ca/e/13970.html>.
- Intergovernmental Panel on Climate Change. Available from: <http://www.ipcc.ch>.
- Medical Council of Canada. Available from: <http://www.mcc.ca>.
- MedTerms. Available from: <http://www.medterms.com>.
- National Advisory Committee on Immunization. Available from: <http://www.phac-aspc.gc.ca/naci-ccni/>.
- Ontario Medical Association. Available from: <https://www.oma.org/HEALTHPROMOTION/OBESITY/Pages/default.aspx>.
- Ontario Ministry of Labour Health and Safety. Available from: <http://www.labour.gov.on.ca/english/hs/>.
- Pan-American Health Organization. Available from: <http://www.paho.org/index.php>.
- Public Health Agency of Canada. Available from: [http://www.phac-aspc.gc.ca/about\\_apropos/index-eng.php](http://www.phac-aspc.gc.ca/about_apropos/index-eng.php).
- WHO, World Health Report 2006. Available from: <http://www.who.int/whr/2006/en/index.html>.
- Workplace Safety and Insurance Board. Available from: <http://www.wsib.on.ca>.
- World Bank. Available from: <http://www.worldbank.org>.

### Evidence-Based Medicine Resources

- Up-to-Date. Available from: <http://www.uptodate.com>.
- Clinical Evidence. Available from: <http://www.clinicalevidence.com>.
- Pier (ACP). Available from: <http://www.pier.acponline.org>.
- OVID EBM Reviews. Available from: <http://gateway.ovid.com/ovidweb.cgi>.
- PubMed – Clinical Queries. Available from: <http://www.ncbi.nlm.nih.gov/pubmed>.
- BMJ Updates plus. Available from: <http://mcmaster.ca/EvidenceUpdates>.
- Users' Guide Series. Available from: <http://www.jamaevidence.com/edguides>.

Aneta Krakowski, Emily McDonough and Tamara Milovic, chapter editors  
 Maria Jogova and Howard Meng, associate editors  
 Melini Gupta, EBM editor  
 Dr. Chloe Leon and Dr. Oshrit Wanono, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Sleep Disorders</b> . . . . .	<b>28</b>
<b>Psychiatric Assessment.</b> . . . .	<b>2</b>	Nocturnal Myoclonus	
History		Narcolepsy	
Mental Status Exam		Primary Insomnia	
Summary of Axes		Sleep Apnea	
<b>Suicide</b> . . . . .	<b>4</b>	<b>Sexuality and Gender</b> . . . . .	<b>28</b>
<b>Psychotic Disorders</b> . . . . .	<b>6</b>	Gender Dysphoria	
Differential Diagnosis of Psychosis		Paraphilias	
Schizophrenia		<b>Eating Disorders</b> . . . . .	<b>29</b>
Schizophreniform Disorder		Anorexia Nervosa	
Brief Psychotic Disorder		Bulimia Nervosa	
Schizoaffective Disorder		<b>Personality Disorders</b> . . . . .	<b>31</b>
Delusional Disorder		<b>Child Psychiatry</b> . . . . .	<b>33</b>
Shared Psychotic Disorder (Folie à Deux)		The Child Psychiatric Interview	
<b>Mood Disorders</b> . . . . .	<b>9</b>	Developmental Concepts	
Mood Episodes		Mood Disorders	
Depressive Disorders		Anxiety Disorders	
Postpartum Mood Disorders		Childhood Schizophrenia	
Bipolar Disorders		Pervasive Developmental Disorders (PDD)	
<b>Anxiety Disorders</b> . . . . .	<b>13</b>	Attention Deficit Hyperactivity Disorder (ADHD)	
Panic Disorder		Oppositional Defiant Disorder (ODD)	
Generalized Anxiety Disorder (GAD)		Conduct Disorder (CD)	
Phobic Disorders		<b>Psychotherapy</b> . . . . .	<b>39</b>
Obsessive-Compulsive Disorder (OCD)		Defense Mechanisms	
Post-Traumatic Stress Disorder (PTSD)		Psychodynamic Therapy	
<b>Adjustment Disorder</b> . . . . .	<b>18</b>	Behaviour Therapy	
<b>Bereavement</b> . . . . .	<b>18</b>	Cognitive Therapy	
<b>Cognitive Disorders</b> . . . . .	<b>19</b>	Cognitive Behavioural Therapy	
Delirium		Dialectical Behavioural Therapy	
Dementia		Other Therapies	
<b>Substance-Related Disorders</b> . . . . .	<b>21</b>	<b>Pharmacotherapy.</b> . . . .	<b>41</b>
Nicotine		Antipsychotics	
Alcohol		Antidepressants	
Opioids		Mood Stabilizers	
Cocaine		Anxiolytics	
Amphetamines		Electroconvulsive Therapy	
Cannabis		Experimental Therapies	
Hallucinogens		<b>Canadian Legal Issues.</b> . . . .	<b>50</b>
"Club Drugs"		Common Forms	
<b>Somatoform Disorders</b> . . . . .	<b>26</b>	Consent	
Body Dysmorphic Disorder		Community Treatment Order (CTO)	
Conversion Disorder		Duty to Inform/Warn	
Hypochondriasis		<b>References</b> . . . . .	<b>52</b>
Pain Disorder			
Somatization Disorder			
<b>Dissociative Disorders.</b> . . . .	<b>27</b>		

Diagnostic Criteria reprinted with permission from the  
 Diagnostic and Statistical Manual of Mental Disorders,  
 Fourth Edition, Text Revision. © 2000 American Psychiatric  
 Association.

## Acronyms

5-HT	serotonin	CD	conduct disorder	IPT	interpersonal therapy	ODD	oppositional defiant disorder
ACT	assertive community treatment	CT	cognitive therapy	MAOI	monoamine oxidase inhibitor	PD	personality disorder
ACh	acetylcholine	DA	dopamine	MDD	major depressive disorder	PDD	pervasive developmental disorder
ADHD	attention deficit hyperactivity disorder	ECT	electroconvulsive therapy	MDE	major depressive episode	PTSD	post-traumatic stress disorder
AN	anorexia nervosa	EPS	extrapyramidal symptoms	MSE	mental status examination	SNRI	serotonin and norepinephrine reuptake inhibitors
ASPD	antisocial personality disorder	EtOH	ethanol/alcohol	NOS	not otherwise specified	SSRI	selective serotonin reuptake inhibitor
BN	bulimia nervosa	GAD	generalized anxiety disorder	OCD	obsessive-compulsive disorder	TCA	tricyclic antidepressant
CBT	cognitive behavioural therapy	GMC	general medical condition	OCPD	obsessive-compulsive personality disorder		

**N.B. The content in this chapter does not reflect the changes made to diagnostic criteria in the DSM-V**

## Psychiatric Assessment



### History

#### Identifying Data

- name, sex, age, ethnicity, marital status, religion, occupation, education, type of residence, with whom they are living, referral source

#### Reliability of Patient as a Historian

- may need collateral source (e.g. parent, teacher) if patient unable/unwilling to co-operate

#### Chief Complaint

- in patient's own words, duration

#### History of Present Illness

- reason for seeking help (that day), current symptoms (onset, duration and course), stressors, supports, functional status, relevant associated symptoms (pertinent positives and negatives)
- safety screen: is the patient endangering self or others? dependents at home (e.g. children, pets), ability to drive safely, ability to care for self (e.g. eating, hygiene, taking medications)

#### Psychiatric Functional Inquiry

- mood: depressed, manic
- anxiety: worries, obsessions, compulsions, panic attacks, phobias, history of trauma
- psychosis: hallucinations, delusions, thought form disorders
- suicide/homicide: ideation, plan, intent, history of attempts
- organic: EtOH/drug use or withdrawal, illness, dementia

#### Past Psychiatric History

- all previous psychiatric diagnoses, psychiatric contacts, treatments (pharmacological and non-pharmacological) and hospitalizations
- also include past suicide attempts, substance use/abuse, and legal problems

#### Past Medical/Surgical History

- all medical, surgical, neurological (e.g. head trauma, seizures), and psychosomatic illnesses
- medications, allergies

#### Family Psychiatric/Medical History

- family members: ages, occupations, personalities, medical or genetic illnesses and treatments, relationships with parents/siblings
- family psychiatric history: any past or current psychiatric illnesses and hospitalizations, suicide, substance abuse

#### Past Personal History

- prenatal and perinatal history (desired vs. unwanted pregnancy, maternal and fetal health, domestic violence, maternal substance use, complications of pregnancy/delivery)
- early childhood to age 3 (developmental milestones, activity/attention level, family stability, attachment figures)
- middle childhood to age 11 (school performance, peer relationships, fire-setting, stealing, incontinence)
- late childhood to adolescence (drug/alcohol, legal problems, peer and family relationships)
- physical or sexual abuse in childhood/adolescence
- adulthood (education, occupations, relationships)
- psychosexual history (paraphilias, gender roles, sexual abuse, sexual dysfunction)
- personality before current illness, recent changes in personality



#### Screening Questions for Major Psychiatric Disorders

- Have you been feeling down, depressed or hopeless?
- Do you feel anxious or worry about things?
- Has there been a time in your life where you have felt euphoric, extremely talkative, had a lot of energy, and a decreased need for sleep?
- Do you see or hear things that you think other people cannot?
- Have you ever thought of harming yourself or committing suicide?



#### Psychiatric Functional Inquiry

##### MOAPS

##### Mood

Organic (e.g. substances and organic disease)

##### Anxiety

##### Psychosis

##### Safety



**Always Remember to Ask About Abuse**  
See [Family Medicine](#), FM28.

## Mental Status Exam (MSE)

### General Appearance and Behaviour

- dress, grooming, posture, gait, physical characteristics, body habitus, apparent vs. chronological age, facial expression (e.g. sad, suspicious)
- psychomotor activity (agitation, retardation), abnormal movements or lack thereof (tremors, akathisia, tardive dyskinesia, paralysis), attention level and eye contact, attitude toward examiner (ability to interact, level of co-operation)

### Speech

- rate (e.g. pressured, slowed), rhythm/fluency, volume, tone, articulation, quantity, spontaneity

### Mood and Affect

- mood: subjective emotional state (in patient's own words)
- affect: objective emotional state inferred from emotional responses to stimuli. Described in terms of:
  - quality (euthymic, depressed, elevated, anxious)
  - range (full, restricted, flat, blunted)
  - stability (fixed, labile)
  - mood congruence (inferred by reader by comparing mood and affect descriptions)
  - appropriateness to thought content

### Thought Process

- coherence (coherent, incoherent)
- logic (logical, illogical)
- stream
  - goal-directed
  - circumstantial: speech that is indirect and delayed in reaching its goal; eventually comes back to the point
  - tangential: speech is oblique or irrelevant; does not come back to the original point
  - loosening of associations: illogical shifting between topics
  - flight of ideas: quickly skipping from one idea to another where the ideas are marginally connected, associated with mania
  - word salad: jumble of words lacking meaning or logical coherence
- perseveration: repetition of the same verbal or motor response to stimuli
- echolalia: repetition of phrases or words spoken by someone else
- thought blocking: sudden cessation of flow of thought and speech
- clang associations: speech based on sound such as rhyming or punning
- neologism: use of novel words or of existing words in a novel fashion

### Thought Content

- suicidal ideation/homicidal ideation
  - frequency and pervasiveness of thoughts, formulation of plan, means to plan, intent, active vs. passive, protective factors
- pre-occupations, ruminations: reflections/thoughts at length, not fixed or false
- obsession: recurrent and persistent thought, impulse or image which is intrusive or inappropriate
  - cannot be stopped by logic or reason
  - causes marked anxiety and distress
  - common themes: contamination, orderliness, sexual, pathological doubt/worry/guilt
- magical thinking: belief that thinking something will make it happen; normal in children
- ideas of reference: similar to delusion (fixed false belief), but the reality of the belief is questioned
- overvalued ideas: unusual/odd beliefs that are not of delusional proportions
- first rank symptoms of schizophrenia: thought insertion/withdrawal/broadcasting
- delusion: a fixed false belief that is out of keeping with a person's cultural or religious background and is firmly held despite incontrovertible proof to the contrary

### Perception

- hallucination: sensory perception in the absence of external stimuli that is similar in quality to a true perception
  - auditory (most common), visual, gustatory, olfactory, tactile
- illusion: misperception of a real external stimulus
- depersonalization: change in self-awareness such that the person feels unreal, detached from his or her body, and/or unable to feel emotion
- derealization: feeling that the world/outer environment is unreal



#### Mental Status Exam

##### ASEPTIC

Appearance and behaviour  
Speech  
Emotion (mood and affect)  
Perception  
Thought content and process  
Insight and judgment  
Cognition



The MSE is analogous to the physical exam. It focuses on current signs, affect, behaviour and cognition.



#### Spectrum of Affect

Full > Restricted > Blunted > Flat



There is poor correlation between clinical impression of suicide risk and frequency of attempts.



#### Delusions

- Persecutory: belief that others are trying to cause harm to you
- Reference: interpreting publicly known events/celebrities as having direct reference to you
- Erotomania: belief that another is in love with you
- Grandiose: an inflated sense of self-worth or power
- Religious: belief of receiving instructions/powers from a higher being; of being a higher being
- Somatic: belief that you have a physical disorder/defect
- Nihilistic: belief that things do not exist; a sense that everything is unreal



#### Cognitive Assessment

Use MMSE to assess:

- Orientation (time and place)
- Memory (immediate and delayed recall)
- Attention and concentration
- Language (comprehension, reading, writing, repetition, naming)
- Spatial ability (intersecting pentagons)

Gross screen for cognitive dysfunction:  
Total score is out of 30; <24 abnormal, 20-24 mild, 10-19 moderate, <10 severe



## Cognition

- level of consciousness
- orientation: time, place, person
- memory: immediate, recent, remote
- global evaluation of intellect (below average, average, above average)
- intellectual functions: attention, concentration, calculation, abstraction (proverb interpretation, similarities test), language, communication

## Insight

- patient's ability to realize that he or she has a physical or mental illness and to understand its implications

## Judgement

- patient's ability to understand relationships between facts and draw conclusions that determine one's actions



### Assessing Insight and Judgement

#### Insight

- Do you think that you have a mental illness?
- Why are you taking this medication?
- Why are you in the hospital?

#### Judgement

Can be observed from collected history and patient's appearance and actions.

- Is he/she dressed appropriately for the weather?
- Is he/she acting appropriately in the given situation?
- Is he/she taking care of self and/or dependents?



### Axis V: Global Assessment of Functioning

The description of each 10-point range in the GAF scale has two components: the first part covers symptom severity, and the second part covers functioning. It should be noted that in situations where the individual's symptom severity and functioning are discordant, the final GAF rating always reflects the worse of the two.

91-100	Superior functioning in a wide range of activities
81-90	Absent or minimal symptoms
71-80	If symptoms are present, they are transient and expected reactions to psychosocial stressors
61-70	Some mild symptoms or some difficulty but generally functioning well
51-60	Moderate symptoms or difficulty
41-50	Serious symptoms or difficulty
31-40	Some impairment in reality testing/communication, impairment in several areas
21-30	Behaviour is influenced by delusions/hallucinations or serious impairment in communication/judgment
11-20	Some danger of hurting self or others or occasionally fails to maintain minimal hygiene or gross impairment in communication
1-10	Persistent danger of severely hurting self or others or persistent inability to maintain minimal personal hygiene or serious suicidal act
0	Inadequate information



### Suicide Risk Factors

#### SAD PERSONS

**Sex** (male)

**Age** >60 yr old

**Depression**

**Previous attempts**

**Ethanol abuse**

**Rational thinking loss** (delusions, hallucinations, hopelessness)

**Suicide in family**

**Organized plan**

**No spouse** (no support systems)

**Serious illness, intractable pain**

## Summary of Axes

### Multiaxial Assessment

- **Axis I**
  - differential diagnosis of DSM-IV clinical disorders
- **Axis II**
  - personality disorders, developmental disability
- **Axis III**
  - general medical conditions that are potentially relevant to the understanding or management of the mental disorder
- **Axis IV**
  - psychosocial and environmental issues
- **Axis V**
  - Global Assessment of Functioning (GAF, 0 to 100) incorporating effects of axes I to IV

### Formulation

- summary outlining current issues and interrelations between an individual's biological, psychological, and social factors
- for each category: predisposing, precipitating, perpetuating, and protecting factors

### Approach to Management

- biological (e.g. pharmacotherapy), psychological [e.g. cognitive behavioural therapy (CBT)], social (e.g. support group)

## Suicide

### Epidemiology

- attempted:completed = 20:1
- M:F = 1:4 for attempts, 3:1 for completed

### Risk Factors

- epidemiologic factors
  - age: increases after age 14, second most common cause of death for ages 15-24, highest rates in persons >65 yr
  - sex: male
  - race/ethnic background: white or native Canadians on reserves
  - marital status: widowed/divorced
  - living situation: alone; no children <18 yr old in the household
  - other: stressful life events, access to firearms
- psychiatric disorders
  - mood disorders (15% lifetime risk in depression; higher in bipolar)
  - anxiety disorders (especially panic disorder)
  - schizophrenia (10-15% risk)
  - substance abuse (especially alcohol – 15% lifetime risk)
  - eating disorders (5% lifetime risk)
  - adjustment disorder
  - conduct disorder
  - personality disorders (borderline, antisocial)
- past history
  - prior suicide attempt
  - family history of suicide attempt/completion

## Clinical Presentation

- symptoms associated with suicide:
  - hopelessness
  - anhedonia
  - insomnia
  - severe anxiety
  - impaired concentration
  - psychomotor agitation
  - panic attacks

## Approach

### Every Patient: "Have you had any thoughts of wanting to hurt or kill yourself?"

- passive ideation: would rather not be alive but has no active plan for suicide
  - ♦ e.g. "I'd rather not wake up" or "I would not mind if a car hit me"
- active ideation
  - ♦ e.g. "I think about killing myself"
- plan: "Do you have a plan as to how you would end your life?"
- intent: "You talk about wanting to die, but are you planning to do this?" or "What has stopped you from ending your life?"
- past attempts: highest risk if previous attempt in past year
  - ♦ ask about lethality, outcome, medical intervention

## Assessment of Suicidal Ideation

- onset and frequency of thoughts: "When did this start?" or "How often do you have these thoughts?"
- control over suicidal ideation: "Can you stop the thoughts or call someone for help?"
- lethality: "Do you want to end your life?" or "What do you think would happen if you actually took those pills?"
- access to means: "How will you get a gun?" or "Which bridge do you think you would go to?"
- time and place: "Have you picked a date and place? Is it in an isolated location?"
- provocative factors: "What makes you feel worse (e.g. being alone)?"
- protective factors: "What keeps you alive (e.g. friends, family, pets, faith, therapist)?"
- final arrangements: "Have you written a suicide note? Made a will? Given away your belongings?"
- practiced suicide or aborted attempts: "Have you put the gun to your head?" "Held the medications in your hand?" "Stood at the bridge?"
- ambivalence: "There must be a part of you that wants to live, after all you came here for help"

## Assessment of Suicide Attempt

- setting (isolated vs. others present, chance of discovery)
- planned vs. impulsive attempt, triggers/stressors
- intoxication
- medical attention (brought in by another person vs. brought in by self to ER)
- time lag from suicide attempt to ER arrival
- expectation of lethality, dying
- reaction to survival (guilt/remorse vs. disappointment/self-blame)

## Management

- proper documentation of the clinical encounter and rationale for management is essential
- higher risk (hospitalization needs to be strongly considered)
  - patients with a plan, access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder
  - do not leave patient alone; remove potentially dangerous objects from room
  - if patient refuses to be hospitalized, complete form for involuntary admission (Form 1)
- lower risk
  - patients who are not actively suicidal, with no plan or access to lethal means
  - discuss protective factors and supports in their life, remind them of what they live for, promote survival skills that helped them through previous suicide attempts
  - make a safety plan: an agreement that they will:
    - ♦ not harm themselves
    - ♦ avoid alcohol, drugs, and situations that may trigger suicidal thoughts
    - ♦ follow-up with you at a designated time
    - ♦ contact a health care worker, call a crisis line or go to an emergency department if they feel unsafe or if their suicidal feelings return or intensify
- depression: consider hospitalization if symptoms severe or if psychotic features are present; otherwise outpatient treatment with good supports and SSRIs/SNRIs
- alcohol-related: usually resolves with abstinence for a few days; if not, suspect depression
- personality disorders: crisis intervention/confrontation, may or may not hospitalize
- schizophrenia/psychosis: hospitalization might be necessary
- parasuicide/self-mutilation: long-term psychotherapy with brief crisis intervention when necessary



### Pharmacotherapy and Suicide Risk

Once antidepressant therapy is initiated, patients should be followed frequently as there is a "suicide window" in which the patient may still be depressed, but now has enough energy to carry out suicide. Avoid tricyclic antidepressants (TCAs) because of high lethality in overdose!



### Suicidal Ideation Assessment

- Asking patients about suicide will not give them the idea or the incentive to commit suicide
- The best predictor of completed suicide is a history of attempted suicide
- The most common psychiatric disorders associated with completed suicide are mood disorders and alcohol abuse

# Psychotic Disorders



## Definition

- characterized by a significant impairment in reality testing
  - delusions or hallucinations (with/without insight into their pathological nature)
  - behaviour so disorganized that it is reasonable to infer that reality testing is disturbed

**Table 1. Differentiating Psychotic Disorders**

Disorder	Psychotic Symptoms	Duration
Brief psychotic disorder	≥1 positive symptoms of criterion A	<1 mo
Schizophreniform disorder	Criterion A	1-6 mo
Schizophrenia	Criterion A	>6 mo
Schizoaffective disorder	≥2 wk (with no mood symptoms)	>1 mo
Delusional disorder	Non-bizarre delusions, hallucinations	>1 mo
2° to substance intoxication/withdrawal	Criterion A	During intoxication or ≤1 mo after withdrawal
2° to mood disorder	Delusions/hallucinations (mood congruent)	Unspecified

### Duration of Time Differentiates the following 3 Psychotic Disorders

Brief Psychotic Disorder <1 month	Schizophreniform Disorder 1-6 months	Schizophrenia >6 months
		→

**Figure 1. Differentiating psychotic disorders with duration**

## Differential Diagnosis of Psychosis

- primary psychotic disorders: schizophrenia, schizophreniform, brief psychotic, schizoaffective, shared psychotic, delusional disorder
- mood disorders: depression with psychotic features, bipolar disorder (mania or depression with psychotic features)
- personality disorders: schizotypal, schizoid, borderline, paranoid, obsessive-compulsive
- general medical conditions: tumour, head trauma, dementia, delirium, metabolic, infection, stroke, temporal lobe epilepsy
- substance-induced psychosis: intoxication or withdrawal, prescribed medications, toxins



### Differential Diagnosis of Psychosis

#### GASPP

General medical condition  
Affective disorders  
Substance induced  
Psychotic disorders  
Personality disorders



### Management of Acute Psychosis and Mania

- Ensure safety of self, patient and other patients
- Have an exit strategy
- Decrease stimulation
- Assume a non-threatening stance
- IM medications (benzodiazepine + antipsychotic) often needed as patient may refuse oral medication
- Physical restraints may be necessary
- Do not use antidepressants or stimulants



### Suggested Criteria for Prodromal Syndromes

- Attenuated positive symptom syndrome: Abnormal/unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and/or organization of communication; onset or worsening in past year
- Brief intermittent psychotic syndrome: Frankly psychotic, unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and/or organization of communication; onset in past 3 mo
- Genetic risk plus functional deterioration: First-degree relative with history of any psychotic disorder or schizotypal personality disorder in patient; substantial functional decline in past year

Adapted from Sadock BJ and Sadock VA. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*, 8th Ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

## Schizophrenia

### DSM-IV-TR Diagnostic Criteria for Schizophrenia

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- characteristic symptoms (active phase): ≥2 of the following, each present for a significant portion of time during a 1-mo period (or less if successfully treated)
  - delusions
  - hallucinations
  - disorganized speech (e.g. frequent derailment or incoherence)
  - grossly disorganized or catatonic behaviour
  - negative symptoms [e.g. affective flattening, alogia (inability to speak), or avolition (inability to initiate and persist in goal-directed activities)]
- only 1 "A" symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behaviour or thoughts, or 2 or more voices conversing with each other
- social/occupational dysfunction: ≥1 major areas of functioning (work, interpersonal relations, self-care) markedly below the level achieved prior to the onset of symptoms
- continuous signs of disturbance for ≥6 mo, including ≥1 mo of active phase symptoms; may include prodromal or residual phases
- schizoaffective and mood disorders excluded
- the disturbance is not due to the direct physiological effects of a substance or a GMC
- if history of pervasive developmental disorder, additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 mo

### Subtypes

- paranoid
  - preoccupation with delusions (typically persecutory or grandiose) or frequent auditory hallucinations
  - relative preservation of cognitive functioning and affect; onset tends to be later in life; believed to have the best prognosis

- catatonic
  - at least two of: motor immobility (catalepsy or stupor); excessive motor activity (purposeless); extreme negativism (resistance to instructions/attempts to be moved) or mutism; peculiar voluntary movement (posturing, stereotyped movements, prominent mannerisms); echolalia or echopraxia (copying another's speech or movement)
- disorganized
  - disorganized speech and behaviour; flat or inappropriate affect
  - poor premorbid personality, early and insidious onset, and continuous course without significant remissions
- undifferentiated
  - meets criteria for schizophrenia, but does not fall into the 3 previous subtypes
- residual
  - no longer have prominent delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour
  - continuing evidence of residual illness such as negative symptoms or attenuated symptoms of criteria A

### Epidemiology

- prevalence: 0.5%-1%; M:F = 1:1
- mean age of onset: females ~27; males ~21

### Etiology

- multifactorial: disorder is a result of interaction between both biological and environmental factors
  - genetic: 40% concordance in monozygotic (MZ) twins; 46% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected
  - neurochemistry ("dopamine hypothesis" theory): excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis while decreased dopamine in the prefrontal cortex may mediate negative and cognitive symptoms. GABA, glutamate and ACh dysfunction are also thought to be involved
  - neuroanatomy: decreased frontal lobe function; asymmetric temporal/limbic function; decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytoarchitectural abnormalities
  - neuroendocrinology: abnormal growth hormone, prolactin, cortisol, and ACTH
  - neuropsychology: global defects seen in attention, language, and memory suggest lack of connectivity of neural networks
  - environmental: indirect evidence of cannabis use, geographical variance, winter season of birth, obstetrical complications, and prenatal viral exposure

### Pathophysiology

- neurodegenerative theory
  - natural history may be a rapid or gradual decline in function and ability to communicate
  - glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
- neurodevelopmental theory: abnormal development of the brain from prenatal life
  - neurons fail to migrate correctly, make inappropriate connections, and break down in later life
  - inappropriate apoptosis during neurodevelopment resulting in faulty connections between neurons

### Management of Schizophrenia

- biological
  - acute treatment and maintenance with antipsychotics ± anticonvulsants ± anxiolytics
- psychosocial
  - psychotherapy (individual, family, group): supportive, CBT (see CBT, PS41)
  - assertive community treatment (ACT): mobile mental health teams that provide individualized treatment in the community and help patients with medication adherence, basic living skills, social support, job placements, and community resources
  - social skills training, employment programs, disability benefits
  - housing (group home, boarding home, transitional home)

### Course and Prognosis

- the majority of individuals display some type of prodromal phase
- course is variable: some individuals have exacerbations and remissions and others remain chronically ill; accurate prediction of the long term outcome is not possible
- early in the illness, negative symptoms may be prominent; positive symptoms appear and typically diminish with treatment; negative symptoms may become more prominent and more disabling
- over time: 1/3 improve, 1/3 remain the same, 1/3 worsen



#### Relationship Between Duration of Untreated Psychosis (DUP) and Outcome in First-episode Schizophrenia

*Am J Psychiatry* 2005;162:1785-1804

**Purpose:** To review the association between DUP and symptom severity at first treatment contact, and between DUP and treatment outcomes.

**Study Characteristics:** Critical review and meta-analysis of 43 studies with 4177 patients.

**Participants:** Patients with non-affective psychotic disorders at or close to first treatment.

**Results:** Shorter DUP was associated with greater response to antipsychotic treatment, as measured by global psychopathology, positive symptoms, negative symptoms, and functional outcomes. At the time of treatment initiation, longer DUP was associated with the severity of negative symptoms but not with the severity of positive symptoms, global psychopathology, or neurocognitive function.

**Conclusions:** DUP may be a potentially modifiable prognostic factor.



#### Supportive Evidence for Dopamine Hypothesis

- DA agonists exacerbate schizophrenia
- Antipsychotic drugs act by blocking post-synaptic DA receptors
- Potency of many antipsychotic drugs correlates with D2 blockade of post-synaptic receptors
- Antipsychotic drugs are associated with an increase in the number of D2 and D4 post-synaptic receptors



#### Good Prognostic Factors

- Acute onset
- Later age at onset
- Shorter duration of prodrome
- Female gender
- Good cognitive functioning
- Good premorbid functioning
- No family history
- Presence of affective symptoms
- Absence of structural brain abnormalities
- Good response to drugs
- Good support system

## Schizophreniform Disorder

- **diagnosis:** criteria A, D and E of schizophrenia are met; an episode of the disorder lasts from 1-6 mo. If the symptoms have extended past 6 mo the diagnosis becomes schizophrenia
- **treatment:** similar to acute schizophrenia
- **prognosis:** better than schizophrenia; begins and ends more abruptly; good pre- and post-morbid function

## Brief Psychotic Disorder

- **diagnosis:** acute psychosis (presence of 1 or more positive symptoms in criteria A 1-4 of schizophrenia) lasting from 1 day to 1 mo, with eventual full return to premorbid level of functioning
- can occur after a stressful event or postpartum (see *Postpartum Mood Disorders*, PS12)
- **treatment:** secure environment, antipsychotics, anxiolytics
- **prognosis:** good, self-limiting, should return to pre-morbid function in about 1 mo

## Schizoaffective Disorder

### DSM-IV-TR Diagnostic Criteria for Schizoaffective Disorder

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).  
American Psychiatric Association.

- A. uninterrupted period of illness during which there is either a MDE, manic episode, or a mixed episode concurrent with symptoms meeting criteria A for schizophrenia
  - B. in the same period, delusions or hallucinations for  $\geq 2$  wk in the absence of prominent mood symptoms
  - C. symptoms that meet criteria for a mood episode are present for a substantial portion of total duration of active and residual periods of the illness
  - D. the disturbance is not due to the direct physiological effects of a substance or GMC
- **treatment:** antipsychotics, mood stabilizers, antidepressants
  - **prognosis:** between that of schizophrenia and of mood disorder

## Delusional Disorder

### DSM-IV-TR Diagnostic Criteria for Delusional Disorder

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).  
American Psychiatric Association.

- A. non-bizarre delusions for  $\geq 1$  mo
  - B. criterion A for schizophrenia has never been met (though patient may have tactile or olfactory hallucinations if they are related to the delusional theme)
  - C. functioning not markedly impaired; behaviour not obviously odd or bizarre
  - D. if mood episodes occur concurrently with delusions, total duration has been brief relative to duration of the delusional periods
  - E. the disturbance is not due to the direct physiological effects of a substance or GMC
- **subtypes:** erotomanic, grandiose, jealous, persecutory, somatic, mixed, unspecified
  - **treatment:** psychotherapy, antipsychotics, antidepressants
  - **prognosis:** chronic, unremitting course but high level of functioning



Non-bizarre delusions involve situations that could occur in real life (e.g. being followed, poisoned, loved at a distance).

## Shared Psychotic Disorder (Folie à Deux)

- **diagnosis:** delusion that develops in an individual who is in a close relationship with another person who already has a psychotic disorder with prominent delusions; the delusion is similar in content to that of the other person
- **treatment:** separation of the two people results in the disappearance of the delusion in the healthier member; antipsychotics may play a role
- **prognosis:** good



# Mood Disorders



## Definitions

- mood disorders are defined by the presence of mood episodes
- mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration (e.g. major depressive, manic, mixed, hypomanic)
- types of mood disorders include:
  - depressive (major depressive disorder, dysthymia)
  - bipolar (bipolar I/II disorder, cyclothymia)
  - secondary to GMC, substances, medications

**Table 2. Secondary Causes of Mood Disorders**

Category	Examples
<b>V</b> Vascular	Cardiomyopathy, CHF, MI, CVA
<b>I</b> Infectious	Encephalitis/meningitis, hepatitis, TB, syphilis, HIV/AIDS
<b>N</b> Neoplastic	Pancreatic cancer, carcinoid, pheochromocytoma, CNS tumour
<b>D</b> Degenerative	Huntington's disease, multiple sclerosis, tuberous sclerosis, degenerative (vascular, Alzheimer's dementia)
<b>I</b> Intoxication/Drugs/Deficiencies	Antihypertensives, antiparkinsonian, hormones, steroids, antituberculous, interferon, antineoplastic medications, vitamin deficiencies (Wernicke's encephalopathy, beriberi, pellagra, pernicious anemia)
<b>C</b> Congenital	—
<b>A</b> Autoimmune	SLE, polyarteritis nodosa
<b>T</b> Traumatic	—
<b>E</b> Endocrine/Metabolic	Hypothyroidism, hyperthyroidism, hypopituitarism, SIADH, porphyria, Wilson's disease, diabetes

## Medical Workup of Mood Disorder

- **routine screening:** physical examination, CBC, thyroid function test, electrolytes, extended electrolytes, urinalysis, drug screen
- **additional screening:** neurological consultation, chest x-ray, ECG, CT

# Mood Episodes

## DSM-IV-TR Criteria for Major Depressive Episode

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- A.  $\geq 5$  of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia)

**Note:** Do not include symptoms that are clearly due to a GMC, mood-incongruent delusions or hallucinations

- depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
  - markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
  - significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
  - insomnia or hypersomnia nearly every day
  - psychomotor agitation or retardation nearly every day
  - fatigue or loss of energy nearly every day
  - feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
  - diminished ability to think or concentrate, or indecisiveness, nearly every day
  - recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
- B. the symptoms do not meet criteria for a mixed episode (see PS10)
- C. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- D. the symptoms are not due to the direct physiological effects of a substance or a GMC
- E. the symptoms are not better accounted for by bereavement; the symptoms persist for longer than 2 mo; symptoms are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation



### Criteria for Depression ( $\geq 5$ )

#### MSIGECAPS

**M**ood: depressed  
**S**leep: increased/decreased  
**I**nterest: decreased  
**G**uilt  
**E**nergy: decreased  
**C**oncentration: decreased  
**A**ppetite: increased/decreased  
**P**sychomotor: agitation/retardation  
**S**uicidal ideation



**DSM-IV-TR Criteria for Manic Episode**

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).  
American Psychiatric Association.

- A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting  $\geq 1$  wk (or any duration if hospitalization is necessary) (note: in DSM-5, "persistently increased goal-directed activity or energy" has been added to criteria A)
  - B. during the period of mood disturbance,  $\geq 3$  of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree:
    - inflated self-esteem or grandiosity
    - decreased need for sleep (e.g. feels rested after only 3 h of sleep)
    - more talkative than usual or pressure to keep talking
    - flight of ideas or subjective experience that thoughts are racing
    - distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
    - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
    - excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained shopping sprees, sexual indiscretions, or foolish business investments)
  - C. the symptoms do not meet criteria for a mixed episode (see below)
  - D. the mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
  - E. the symptoms are not due to the direct physiological effects of a substance (e.g. drug of abuse, medication, or other treatment) or a GMC (e.g. hyperthyroidism).
- Note:** Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g. medication, ECT therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder (this has been removed in DSM-5)

**Criteria for Mania ( $\geq 3$ )****GST PAID**

Grandiosity

Sleep (decreased need)

Talkative

Pleasurable activities, Painful consequences

Activity

Ideas (flight of)

Distractible

**Mixed Episode**

- criterion met for both manic episode and MDE nearly every day for 1 wk
- criteria D and E of manic episodes are met
- **Note:** in DSM-5, mixed episode is no longer a separate mood diagnosis; instead, depressed episodes and manic episodes can have a "with mixed features" specifier

**Hypomanic Episode**

- criterion A of a manic episode is met, but duration is  $\geq 4$  d
- criteria B and E of manic episodes are met
- episode associated with an uncharacteristic decline in functioning that is observable by others
- change in function is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features

## Depressive Disorders

**MAJOR DEPRESSIVE DISORDER****DSM-IV-TR Diagnostic Criteria for Major Depressive Disorder (MDD), Single Episode (vs. Recurrent)**

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).  
American Psychiatric Association.

- A. presence of a single MDE (vs. recurrent, which requires presence of two or more MDEs; to be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a MDE)
  - B. the MDE is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS
  - C. there has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode
- **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of a GMC

**Features/Specifiers**

- **psychotic:** with hallucinations or delusions
- **chronic:** lasting 2 yr or more
- **catatonic:** at least two of: motor immobility, excessive motor activity, extreme negativism or mutism, peculiarities of voluntary movement, echolalia or echopraxia
- **melancholic:** quality of mood is distinctly depressed, mood is worse in the morning, early morning awakening, marked weight loss, excessive guilt, psychomotor retardation
- **atypical:** increased sleep, weight gain, leaden paralysis, rejection hypersensitivity
- **postpartum:** (see *Postpartum Mood Disorders*, PS12)
- **seasonal:** pattern of onset at the same time each year (most often in the fall or winter)
- **Note:** in DSM-5 the specifiers have changed to include: with anxious distress, with mixed features, with melancholic features, with atypical features, with mood-congruent psychotic features, with mood-incongruent psychotic features, with catatonia, with peripartum onset, with seasonal pattern

## Epidemiology

- prevalence: 12.2%
  - lifetime prevalence: male 2.9%, female 5%
  - annual prevalence: peak prevalence age 15-25 yr (M:F = 1:2)

## Etiology

- biological
  - genetic: 65-75% MZ twins; 14-19% DZ twins
  - neurotransmitter dysfunction: decreased activity of 5HT, NE and DA at the level of the synapse; changes in GABA and glutamate; changes in brain circuitry
  - neuroendocrine dysfunction: increased production of corticotropin causing excessive HPA axis activity
  - neuroanatomy: smaller frontal lobes and hippocampal volume; increased ventricle sizes
  - neurophysiologic: decreased REM latency and slow-wave sleep; increased REM length
  - secondary to GMC
- psychosocial
  - psychodynamic (e.g. low self-esteem)
  - cognitive (e.g. negative thinking)
  - environmental factors (e.g. job loss, bereavement, history of abuse, early life adversity)
  - co-morbid psychiatric diagnoses (e.g. anxiety, substance abuse, developmental disability, dementia, eating disorder)

## Risk Factors

- sex: female > male
- age: onset between 25-50 yr of age
- family history: depression, alcohol abuse, sociopathy
- childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
- personality: insecure, dependent, obsessional
- recent stressors: illness, financial, legal
- postpartum <6 mo
- lack of intimate, confiding relationships or social isolation

## Depression in the Elderly

- affects about 15% of community residents >65 yr old; up to 50% in nursing homes
- high suicide risk due to social isolation, chronic medical illness
- suicide peak: males aged 80-90; females aged 50-65
- dyphoria may not be a reliable indicator of depression in those >85 yr
- often present with somatic complaints (e.g. changes in weight, sleep, energy) or anxiety symptoms
- may have prominent cognitive changes after onset of mood symptoms (dementia syndrome of depression)
- refer to Table 4 (see *Dementia*, PS21) to compare with delirium and dementia

## Treatment

- biological: antidepressants primarily; could also consider lithium, antipsychotics, anxiolytics, light therapy, ECT, repetitive transcranial magnetic stimulation (rTMS)
- psychological
  - individual therapy (psychodynamic, interpersonal, CBT), family therapy, group therapy
- social: vocational rehabilitation, social skills training
- experimental: magnetic stimulation therapy (MST), deep brain stimulation, vagal nerve stimulation
- studies suggest CBT with pharmacotherapy results in better outcomes

## Prognosis

- one year after diagnosis of a MDE without treatment: 40% of individuals still have symptoms that are sufficiently severe to meet criteria for a full MDE, 20% continue to have some symptoms that no longer meet criteria for a MDE, 40% have no mood disorder

## DYSTHYMIA

### DSM-IV-TR Diagnostic Criteria for Dysthymic Disorder

**Note: in DSM-5 this has been changed to Persistent Depressive Disorder**

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for  $\geq 2$  yr  
Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr
- presence, while depressed, of  $\geq 2$  of the following
  - poor appetite or overeating
  - insomnia or hypersomnia
  - low energy or fatigue



### Antidepressants for Depression in Medical Illness

*Cochrane DB Syst Rev* 2010; Issue 3

This systematic review and meta-analysis of 51 RCTs (3603 patients) compared antidepressants to placebo in patients with a physical disorder (e.g. cancer, MI) who have been diagnosed as depressed (including major depression, adjustment disorder, and dysthymia).

**Conclusions:** Antidepressants, including SSRIs and TCAs, cause a significant improvement in patients with a physical illness, as compared to placebo.



### St. John's Wort for Major Depression

*Cochrane DB Syst Rev* 2008;4:CD000448

**Study:** Systematic review of trials that were (1) randomized, double-blinded (2) with patients with major depression (3) comparing St. John's wort (hypericum extracts) with placebo or standard antidepressants and (4) included clinical outcomes.

**Patients:** 5489 patients with major depression.

**Outcomes:** 1. Effectiveness: treatment response measured by a depression scale 2. Safety: the proportion of patients who dropped out due to adverse effects.

**Intervention:** St. John's wort vs. placebo; St. John's wort vs. standard antidepressants.

**Results:** 29 trials, 5489 patients, with 18 comparisons with placebo and 17 with antidepressants. St. John's wort is more effective than placebo (response rate ratio = 1.87, 95% CI), and similarly effective as antidepressants (RRR = 1.02, 95% CI). Less adverse effects with hypericum extracts. However, the effect size is dependent on the country of origin.



### Cognitive Therapy vs. Medications in the Treatment of Moderate to Severe Depression

*Arch Gen Psychiatry* 2005;62:409-416

**Study:** Randomized control trial.

**Patients:** 240 outpatients with moderate to severe MDD, aged 18-70.

**Intervention:** 16 wk of paroxetine with or without augmentation with lithium carbonate or desipramine hydrochloride (n=120) versus cognitive behavioural therapy (n=60). Response up to 8 wk was controlled by pill placebo (n=60)

**Main Outcomes:** The Hamilton Depression Rating scale was used to determine response to treatment.

**Results:** At 8 wk, 50% (95%CI 41-59%) of patients on medication and 43% (95%CI 31-56%) of patients on CBT had responded in comparison to 25% (95%CI 16-38%) of patients on pill placebo. There was no significant difference between medication and CBT. At 16 wk, 46% of patients on medication and 40% of patients on CBT achieved remission.

**Summary:** There is no difference in efficacy between CBT vs. paroxetine in the treatment of moderate to severe depression.

- low self-esteem
  - poor concentration or difficulty making decisions
  - feelings of hopelessness
- C. during the 2-yr period (1 yr for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 mo at a time
- D. no MDE has been present during the first 2 yr of the disturbance (1 yr for children and adolescents); i.e. the disturbance is not better accounted for by chronic MDD, or MDD in partial remission
- E. there has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode, and criteria have never been met for Cyclothymic Disorder
- F. the disturbance does not occur exclusively during the course of a chronic psychotic disorder, such as Schizophrenia or Delusional Disorder
- G. the symptoms are not due to the direct physiological effects of a substance or a GMC
- H. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

### Epidemiology

- point prevalence: 3%; life prevalence: 6%; M:F = 1:2-3

### Treatment

- psychological
  - principal treatment for dysthymia
  - individual, group, and family therapy
- biological
  - antidepressant therapy (SSRIs/SNRIs) as an outpatient

## Postpartum Mood Disorders

### Postpartum "Blues"

- transient period of mild depression, mood instability, anxiety, decreased concentration, increased concern over own health and health of baby – considered to be normal emotional changes related to the puerperium
- occurs in 50-80% of mothers; begins 2-4 d postpartum, usually lasts 48 h, can last up to 10 d
- does not require psychotropic medication
- patient at increased risk of developing postpartum depression

### Postpartum Depression (PPD)

- **diagnosis:** MDE, onset within 4 wk postpartum
- **clinical presentation:**
  - typically lasts 2 to 6 mo; residual symptoms can last up to 1 yr
  - may present with psychosis – rare (0.2%), usually associated with mania, but also with MDE
  - severe symptoms include extreme disinterest in baby, suicidal and infanticidal ideation
- **epidemiology:** occurs in 10% of mothers, risk of recurrence 50%
- **risk factors:**
  - previous history of a mood disorder (postpartum or otherwise)
  - psychosocial factors: stressful life events, unemployment, marital conflict, lack of social support, unwanted pregnancy, colicky or sick infant
- **treatment:**
  - psychotherapy (CBT or IPT)
  - short-term safety of maternal SSRIs for breastfeeding infants established; long-term effects unknown
  - if depression severe, consider ECT
- **prognosis:**
  - impact on child development: increased risk of cognitive delay, insecure attachment, behavioural disorders
  - treatment of mother improves outcome for child at 8 mo through increased mother-child interaction



#### Selective Serotonin Reuptake Inhibitors in Pregnancy and Infant Outcomes

*Paediatr Child Health* 2011;16:562-563

Study: Canadian Paediatric Society (CPS) Clinical practice guidelines.

**Recommendations:** It is important to treat depression in pregnancy. There is no evidence that SSRIs increase the risk of major malformations. There is conflicting evidence concerning the association of paroxetine and cardiac malformations. SSRIs are not contraindicated while breast-feeding.

## Bipolar Disorders

### BIPOLAR I / BIPOLAR II DISORDER

#### Definition

- Bipolar I Disorder
  - disorder in which at least one manic or mixed episode has occurred
  - commonly accompanied by at least 1 MDE but not required for diagnosis
- Bipolar II Disorder
  - disorder in which there is at least 1 MDE and at least 1 hypomanic episode
  - no past manic or mixed episodes

### Epidemiology

- prevalence: 0.6-0.9%; M:F = 1:1
- age of onset: teens to 20's

### Risk Factors

- high SES
- genetic: 60-65% of bipolar patients have family history of major mood disorders

### Classification

- classification of bipolar disorder involves describing the current or most recent mood episode as either manic, hypomanic, mixed or depressed
- the current or most recent episode can be further classified as without psychotic features, with psychotic features, with catatonic features, with postpartum onset, with seasonal pattern, with rapid cycling (at least 4 episodes of a mood disturbance in the previous 12 mo that meet criteria for a major depressive, manic, mixed, or hypomanic episode)

### Treatment

- biological: lithium, anticonvulsants, antipsychotics, antidepressants, ECT
- psychological: supportive or psychodynamic psychotherapy, CBT, ITP or interpersonal social rhythm therapy
- social: vocational rehabilitation, consider leave of absence from school/work, consider substitute decision maker for finances, drug and EtOH cessation, sleep hygiene, social skills training, education for family members

### Course and Prognosis

- high suicide rate (15% mortality from suicide)
- relapsing and remitting course with alternating manic and depressive episodes; depressive symptoms tend to occur more frequently and last longer than manic episodes
- patients spend almost half of their lives symptomatic
- may switch rapidly between depression and mania without any period of euthymia in between
- high recurrence rate for mania – 90% will have a subsequent episode in the next 5 yr

## CYCLOTHYMIA

### Diagnosis

- presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for MDE) for  $\geq 2$  yr; never without symptoms for  $>2$  mo
- no MDE, manic or mixed episodes, no evidence of psychosis
- symptoms are not due to the direct physiological effects of a substance or GMC
- symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

### Treatment

- similar to Bipolar I: anticonvulsants  $\pm$  psychotherapy



Patients with bipolar disorder are at higher risk for suicide when they switch from mania to depression, especially as they become aware of consequences of their behaviour during the manic episode.



Treatment of bipolar depression must be done extremely cautiously, as a switch from depression to mania can result; monotherapy with antidepressants should be avoided.



#### A Randomized Controlled Trial of Cognitive Therapy for Bipolar Disorder: Focus on Long-term Change

*J Clin Psychiatry* 2006;67:277-286

**Study:** Randomized, blinded clinical trial.

**Patients:** 52 patients with DSM-IV bipolar 1 or 2 disorder.

**Intervention:** Patients allocated to either a 6 mo trial of cognitive therapy (CT) with emotive techniques or treatment as usual. Both groups received mood stabilizers.

**Main Outcomes:** Relapse rates, dysfunctional attitudes, psychosocial functioning, hopelessness, self-control, medication adherence. Patients were assessed by independent raters blinded to treatment group.

**Results:** At 6 mo, CT patients experienced fewer depressive symptoms and fewer dysfunctional attitudes. There was a non-significant ( $p=.06$ ) trend to greater time to depressive relapse. At 12 mo follow-up, CT patients had lower Young Mania Rating scores and improved behavioural self-control. At 18 mo, CT patients reported less severity of illness.

**Conclusions:** CT appears to provide benefits in the 12 mo after completion of therapy.



## Anxiety Disorders

### Definition

- anxiety is a universal human characteristic involving tension, apprehension, or even terror
- serves as an adaptive mechanism to warn about an external threat by activating the sympathetic nervous system (fight or flight)
- manifestations of anxiety can be described through:
  - physiology: main brain structure involved is the amygdala (fear conditioning); neurotransmitters involved include 5-HT, cholecystokinin, epinephrine, norepinephrine, DA
  - psychology: one's perception of a given situation is distorted which causes one to believe it is threatening in some way
  - behaviour: once feeling threatened, one responds by escaping or facing the situation, thereby causing a disruption in daily functioning
- anxiety becomes pathological when:
  - fear is greatly out of proportion to risk/severity of threat
  - response continues beyond existence of threat or becomes generalized to other similar or dissimilar situations
  - social or occupational functioning is impaired

## Differential Diagnosis

**Table 3. Differential Diagnosis of Anxiety Disorders**

<b>Cardiovascular</b>	Post-MI, arrhythmia, congestive heart failure, pulmonary embolus, mitral valve prolapse
<b>Respiratory</b>	Asthma, COPD, pneumonia, hyperventilation
<b>Endocrine</b>	Hyperthyroidism, pheochromocytoma, hypoglycemia, hyperadrenalism, hyperparathyroidism
<b>Metabolic</b>	Vitamin B <sub>12</sub> deficiency, porphyria
<b>Neurologic</b>	Neoplasm, vestibular dysfunction, encephalitis
<b>Substance-Induced</b>	Intoxication (caffeine, amphetamines, cocaine, thyroid preparations, OTC for colds/decongestants), withdrawal (benzodiazepines, alcohol)
<b>Other Psychiatric Disorders</b>	Psychotic disorders, mood disorders, personality disorders (OCPD), somatoform disorders

## Medical Workup of Anxiety Disorder

- routine screening: physical examination, CBC, thyroid function test, electrolytes, urinalysis, urine drug screening
- additional screening: neurological consultation, chest x-ray, ECG, CT

## Panic Disorder

### DSM-IV-TR Diagnostic Criteria for Panic Disorder without Agoraphobia

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).  
American Psychiatric Association.

- A. both (1) and (2)
- (1) recurrent unexpected panic attacks: a discrete period of intense fear or discomfort, in which  $\geq 4$  of the following symptoms develop abruptly and reach a peak within 10 min
    - ♦ palpitations, pounding heart, or accelerated heart rate
    - ♦ sweating
    - ♦ trembling or shaking
    - ♦ sensations of shortness of breath or smothering
    - ♦ feeling of choking
    - ♦ chest pain or discomfort
    - ♦ nausea or abdominal distress
    - ♦ feeling dizzy, unsteady, lightheaded, or faint
    - ♦ derealization (feelings of unreality) or depersonalization (being detached from oneself)
    - ♦ fear of losing control or going crazy
    - ♦ fear of dying
    - ♦ paresthesias (numbness or tingling sensations), chills or hot flushes
  - (2) at least one of the attacks has been followed by 1 mo (or more) of  $\geq 1$  of the following
    - ♦ persistent concern about having additional attacks
    - ♦ worry about the implications of the attack or its consequences (e.g. losing control, having a heart attack, "going crazy")
    - ♦ a significant change in behaviour related to the attacks
- B. absence of agoraphobia
- C. the panic attacks are not due to the direct physiological effects of a substance or GMC
- D. the panic attacks are not better accounted for by another mental disorder, such as social phobia, specific phobia, obsessive-compulsive disorder, post-traumatic stress disorder, separation anxiety disorder

### Epidemiology

- prevalence: 1.5-5% (one of the top five most common reasons to see a family doctor); M:F = 1:2-3
- onset: average late 20's, familial pattern

### Treatment

- psychological
  - CBT: interoceptive exposure (eliciting symptoms of a panic attack and learning to tolerate the symptoms without coping strategies); cognitive restructuring (addressing underlying beliefs regarding the panic attacks), relaxation techniques (visualization, box-breathing)
- pharmacological
  - SSRIs: fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline
  - SNRI: venlafaxine
  - with SSRI/SNRI start with low doses, titrate up slowly
  - anxiety disorders often require treatment at higher doses for a longer period of time (i.e. up to 8-12 wk than used for depression)
  - to prevent non-compliance due to physical side effects, explain symptoms to expect prior to initiation of therapy
  - other antidepressants (TCAs, mirtazapine, MAOIs)
    - ♦ consider avoiding bupropion due to stimulating effects
  - benzodiazepines (short term, low dose, regular schedule, long half-life, avoid prn use)



#### Pharmacotherapy for Anxiety Disorders in Children and Adolescents

*Cochrane DB Syst Rev* 2009;3:CD005170

**Study:** Systematic review of 22 randomized control trials to assess the efficacy and tolerability of medication for treating pediatric anxiety disorders.

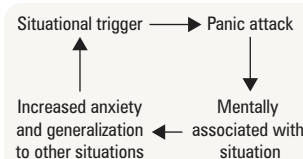
**Methods:** Literature searches of MEDLINE, EMBASE, PsycINFO (1966-2008).

**Patients:** Children/adolescents under the age of 18 diagnosed with any anxiety disorder according to DSM criteria.

**Intervention:** Medication (benzodiazepines, SSRIs and TCAs) vs. placebo.

**Results:** The majority of the trials assessed the efficacy of SSRIs (N = 15). Medication and placebo response occurred in 58.1% and 31.5% of patients, respectively (number of studies = 14).

**Reviewers' Conclusion:** Medication treatments can be effective in pediatric anxiety disorders, acting to reduce core symptoms, and should be considered as part of the treatment of these disorders. The greatest number of trials showing efficacy to date have assessed the SSRIs in treating pediatric OCD. The routine use of benzodiazepines cannot be recommended.



**Figure 2. Panic attack**



#### Criteria for Panic Disorder ( $\geq 4$ )

##### STUDENTS FEAR THE 3 Cs

Sweating  
Trembling  
Unsteadiness, dizziness  
Depersonalization, Derealization  
Excessive heart rate, palpitations  
Nausea  
Tingling  
Shortness of breath

**Fear of dying, losing control, going crazy**

**3 Cs: Chest pain, Chills, Choking**



#### Panic Attack vs. Panic Disorder

Panic disorder consists of panic attacks + other criteria.

Panic attack is not a codable disorder and can occur in the context of many different disorders.



#### Starting Medication for Anxiety

Start low, go slow, aim high and explain symptoms to expect prior to initiation of therapy.



**Prognosis**

- 6-10 yr post-treatment: 30% well, 40-50% improved, 20-30% no change or worse
- clinical course: chronic, but episodic with psychosocial stressors

**Panic Disorder with Agoraphobia**

- agoraphobia
  - anxiety about being in places or situations from which escape might be difficult (or embarrassing) or where help may not be available in the event of having an unexpected panic attack
  - fears commonly involve situations such as being out alone, being in a crowd, standing in a line, or travelling on a bus
- situations are avoided, endured with anxiety or panic, or require companion
- treatment: as per panic disorder

**Generalized Anxiety Disorder (GAD)****DSM-IV-TR Diagnostic Criteria for Generalized Anxiety Disorder**

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance)
- the person finds it difficult to control the worry
- the anxiety and worry are associated with  $\geq 3$  of the following 6 symptoms (with at least some symptoms present for more days than not for the past 6 mo)
 

**Note:** Only one item is required in children

  - restlessness or feeling keyed up or on edge
  - being easily fatigued
  - difficulty concentrating or mind going blank
  - irritability
  - muscle tension
  - sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
- the focus of the anxiety and worry is not confined to features of an Axis I disorder, such as panic disorder, social phobia, etc.
- the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- the disturbance is not due to the direct physiological effects of a substance or a GMC and does not occur exclusively during a Mood Disorder, a Psychotic Disorder, or a Pervasive Developmental Disorder

**Criteria for GAD ( $\geq 3$ )****BE SKIM**

Blank mind  
Easily fatigued  
Sleep disturbance  
Keyed up  
Irritability  
Muscle tension

**Epidemiology**

- 1-yr prevalence: 3-8%; M:F = 1:2
  - if considering only those receiving inpatient treatment, ratio is 1:1
- most commonly presents in early adulthood

**Treatment**

- lifestyle: caffeine and EtOH avoidance, sleep hygiene
- psychological: CBT including relaxation techniques, mindfulness
- biological
  - SSRIs and SNRIs are 1st line (paroxetine, escitalopram, sertraline, venlafaxine XL)
  - 2nd line: bupropion (caution due to stimulating effects), buspirone (tid dosing)
  - add-on benzodiazepines (short term, low dose, regular schedule, long half-life, avoid prn)
  - $\beta$ -blockers not recommended

**Prognosis**

- chronically anxious adults become less so with age
- depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress
- difficult to treat

**Phobic Disorders****Specific Phobia**

- definition: marked and persistent fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
- lifetime prevalence 12-16%; M:F ratio variable
- types: animal/insect, environment (heights, storms), blood/injection/injury, situational (airplane, closed spaces), other (loud noise, clowns)



**Social Phobia (Social Anxiety Disorder)**

- definition: marked and persistent fear of social or performance situations in which one is exposed to unfamiliar people or to possible scrutiny by others; fearing he/she will act in a way that may be humiliating or embarrassing (e.g. public speaking, initiating or maintaining conversation, dating, eating in public)
- lifetime prevalence may be as high as 13-16%; F>M

**Diagnostic Criteria for Phobic Disorders**

- exposure to stimulus almost invariably provokes an immediate anxiety response; may present as a panic attack
- person recognizes fear as excessive or unreasonable
- situations are avoided or endured with anxiety/distress
- significant interference with daily routine, occupational/social functioning, and/or marked distress
- if person is <18 yr, duration is at least 6 mo

**Treatment**

- psychological
  - cognitive behaviour therapy (focusing on both in vivo and virtual exposure therapy – gradually facing feared situations)
  - behavioural therapy is more efficacious than medication
- biological
  - $\beta$ -blockers or benzodiazepines in acute situations (e.g. public speaking)

**Prognosis**

- chronic

## Obsessive-Compulsive Disorder (OCD)

**DSM-IV-TR Diagnostic Criteria for Obsessive Compulsive Disorder**

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).

American Psychiatric Association.

**A. either obsessions or compulsions:****obsessions** as defined by (1), (2), (3), and (4)

- (1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
- (2) the thoughts, impulses, or images are not simply excessive worries about real-life problems
- (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
- (4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed)

**compulsions** as defined by (1) and (2)

- (1) repetitive behaviours or mental acts that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
- (2) the behaviours or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviours or mental acts either are not connected in a realistic way with what they are designed to neutralize/prevent or are clearly excessive

**B. at some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable (ego-dystonic)**

**Note:** This does not apply to children

- C. the obsessions or compulsions cause marked distress, are time-consuming (take  $\geq 1$  h a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships**
- D. if another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g. preoccupation with food in the presence of an Eating Disorder)**
- E. the disturbance is not due to the direct physiological effects of a substance or a GMC**

**Epidemiology**

- lifetime prevalence rates 2-3%; M=F
- rate of OCD in first-degree relatives is higher than in the general population

**Treatment**

- CBT: exposure with response prevention (ERP) – involves exposure to feared situations with the addition of preventing the compulsive behaviours; cognitive strategies include challenging underlying beliefs
- pharmacotherapy: SSRIs/SNRIs, clomipramine; adjunctive risperidone

**Prognosis**

- tends to be refractory and chronic

## Post-Traumatic Stress Disorder (PTSD)

### DSM-IV-TR Diagnostic Criteria for Post-Traumatic Stress Disorder

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).

American Psychiatric Association.

- A. the person has been exposed to a traumatic event in which both of the following were present
  - (1) the person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others
  - (2) the person's response involved intense fear, helplessness, or horror

**Note:** in children, this may be expressed instead by disorganized or agitated behaviour
- B. the traumatic event is persistently re-experienced in one (or more) of the following ways:
  - (1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions

**Note:** in children, repetitive play may occur in which themes or aspects of the trauma are expressed

  - (2) recurrent distressing dreams of the event

**Note:** in children, there may be frightening dreams without recognizable content

  - (3) acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated)

**Note:** in children, trauma-specific reenactment may occur

  - (4) intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
  - (5) physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
- C. persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by  $\geq 3$  of the following:
  - (1) efforts to avoid thoughts, feelings, or conversations associated with the trauma
  - (2) efforts to avoid activities, places, or people that arouse recollections of the trauma
  - (3) inability to recall an important aspect of the trauma
  - (4) markedly diminished interest or participation in significant activities
  - (5) feeling of detachment or estrangement from others
  - (6) restricted range of affect (e.g. unable to have loving feelings)
  - (7) sense of a foreshortened future (e.g. does not expect to have a career, marriage, children, or a normal life span)
- D. persistent symptoms of increased arousal (not present before the trauma), as indicated by  $\geq 2$  of the following:
  - (1) difficulty falling or staying asleep
  - (2) irritability or outbursts of anger
  - (3) difficulty concentrating
  - (4) hypervigilance
  - (5) exaggerated startle response
- E. duration of the disturbance (symptoms in Criteria B, C, and D) is  $\geq 1$  mo
- F. the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

### Epidemiology

- prevalence in general population: 7%
- men's trauma is most commonly combat experience/physical assault; women's trauma is usually physical or sexual assault

### Treatment

- CBT: exposure therapy, challenge dysfunctional beliefs, emotional regulation techniques (e.g. breathing, relaxation)
- biological
  - SSRIs
  - benzodiazepines (for acute anxiety)
  - adjunctive atypical antipsychotics (risperidone, olanzapine)
- Eye Movement Desensitization and Reprocessing (EMDR): an experimental method of reprocessing memories of distressing events by recounting them while using a form of dual attention stimulation such as eye movements, bilateral sound, or bilateral tactile stimulation (its use is controversial because of limited evidence)

### Complications

- substance abuse, relationship difficulties, depression, impaired social and occupational functioning disorders, Axis II disorders



#### Acute Stress Disorder

May be a precursor to PTSD

##### Criteria:

- Exposure to traumatic event
- Dissociative symptoms
- Event is persistently re-experienced
- Avoidance of stimuli
- Symptoms of anxiety or increased arousal
- Causes clinically significant distress or impairment in social, occupational or other important areas of functioning
- Symptoms last 2 d to 4 wk and occur within 4 wk of event



#### Criteria for Post-Traumatic Stress Disorder

##### TRAUMA

Traumatic event

Re-experience the event

Avoidance of stimuli associated with the trauma

Unable to function

More than a Month

Arousal increased

# Adjustment Disorder



## DSM-IV-TR Diagnostic Criteria for Adjustment Disorder

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000).  
American Psychiatric Association.

- A. the development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 mo of the onset of the stressor(s)
- B. these symptoms or behaviours are clinically significant as evidenced by either of the following
  - (1) marked distress that is in excess of what would be expected from exposure to the stressor
  - (2) significant impairment in social or occupational (academic) functioning
- C. the stress-related disturbance does not meet criteria for another Axis I disorder and is not merely an exacerbation of a pre-existing Axis I or Axis II disorder
- D. the symptoms do not represent bereavement
- E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 mo
  - specify if
    - ♦ **acute:** if the disturbance lasts less than 6 mo
    - ♦ **chronic:** if the disturbance lasts for 6 mo or longer
  - adjustment disorders are coded based on the subtype, which is selected according to the predominant symptoms

## Classification

- types of stressors
  - single (e.g. termination of romantic relationship)
  - multiple (e.g. marked business difficulties and marital problems)
  - recurrent (e.g. seasonal business crises)
  - continuous (e.g. living in a crime-ridden neighbourhood)
  - developmental events (e.g. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)
  - **Note:** the specific stressor is specified on Axis IV
- **subtypes**, adjustment disorder with:
  - ♦ depressed mood
  - ♦ anxiety
  - ♦ mixed anxiety and depressed mood
  - ♦ disturbance of conduct
  - ♦ mixed disturbance of emotions and conduct
  - ♦ unspecified

## Epidemiology

- M=F

## Treatment

- brief psychotherapy (group, individual), crisis intervention
- biological
  - benzodiazepines may be used for those with anxiety symptoms (short-term, low-dose, regular schedule)
  - SSRIs for both depression and anxiety symptoms

# Bereavement

## Clinical Presentation

- length and characteristics of “normal” bereavement are variable between individuals/cultures
- may present with symptoms of MDE/MDD but individual regards depressed mood as normal
- diagnosis of MDD only given if symptoms persist >2 mo after loss (note – this stipulation has been removed in DSM-5; it is now possible to diagnose MDD regardless of how close it comes to loss)
- presence of following symptoms may indicate abnormal grief/presence of MDD
  - guilt about things other than actions taken or not taken by the survivor at the time of death
  - thoughts of death other than the survivor feeling that they would be better off dead or should have died with the deceased person; morbid preoccupation with worthlessness
  - marked psychomotor retardation; prolonged and marked functional impairment
  - hallucinatory experiences other than thinking that the survivor hears the voice of or transiently sees the image of the deceased person
- prolonged or complicated grief may occur if unable to “move on” or re-engage in life



### Risk Factors for Poor Bereavement Outcome:

- Poor social supports
- Unanticipated death or lack of preparation for death
- Highly dependent relationship with deceased
- High initial distress
- Other concurrent stresses and losses
- Death of a child
- Pre-existing psychiatric disorders, especially depression and separation anxiety

# Cognitive Disorders



## Delirium

- see [Neurology](#), N17 and [Geriatric Medicine](#), GM3



### DSM-IV-TR Diagnostic Criteria for Delirium due to a GMC

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
- a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia
- the disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
- there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a GMC

### Clinical Presentation and Assessment

- common symptoms
  - wandering attention
  - distractibility
  - disorientation (time, place, rarely person)
  - misinterpretations, illusions, hallucinations
  - speech/language disturbances (dysarthria, dysnomia, dysgraphia)
  - affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
  - shifts in psychomotor activity (groping/picking at clothes, attempts to get out of bed when unsafe, sudden movements, sluggishness, lethargy)
- Folstein Mini Mental Status Exam (see sidebar, PS3) is helpful to assess baseline of altered mental state (i.e. score will improve as symptoms resolve)

### Risk Factors

- hospitalization (incidence 10-40%)
- nursing home residents (incidence 60%)
- childhood (e.g. febrile illness, anticholinergic use)
- old age (especially males)
- severe illness (e.g. cancer, AIDS)
- pre-existing cognitive impairment or brain pathology
- recent anesthesia
- substance abuse

### Etiology

- Infectious (encephalitis, meningitis, UTI, pneumonia)
- Withdrawal (alcohol, barbiturates, benzodiazepines)
- Acute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
- Trauma (head injury, postoperative)
- CNS pathology (stroke, hemorrhage, tumour, seizure disorder, Parkinson's)
- Hypoxia (anemia, cardiac failure, pulmonary embolus)
- Deficiencies (vitamin B<sub>12</sub>, folic acid, thiamine)
- Endocrinopathies (thyroid, glucose, parathyroid, adrenal)
- Acute vascular (shock, vasculitis, hypertensive encephalopathy)
- Toxins: substance use, sedatives, opioids (especially morphine), anesthetics, anticholinergics, anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
- Heavy metals (arsenic, lead, mercury)

### Investigations

- standard: CBC and differential, electrolytes, Ca<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup>, Mg<sup>2+</sup>, glucose, ESR, LFTs, Cr, BUN, TSH, vitamin B<sub>12</sub>, folate, albumin, urine C&S, R&M
- as indicated: ECG, CXR, CT head, toxicology/heavy metal screen, VDRL, HIV, LP, EEG (typically abnormal: generalized slowing or fast activity), blood cultures
- indications for CT head: focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, history of cancer



#### Delirium

#### I WATCH DEATH

Infectious

Withdrawal from drugs

Acute metabolic disorder

Trauma

CNS pathology

Hypoxia

Deficiencies in vitamins

Endocrinopathies

Acute vascular insults

Toxins

Heavy metals

## Management

- intrinsic
  - identify and treat underlying cause immediately
  - stop all non-essential medications
  - maintain nutrition, hydration, electrolyte balance and monitor vitals
- extrinsic
  - environment should be quiet and well lit
  - optimize hearing and vision
  - room near nursing station for closer observation; constant care if patient jumping out of bed, pulling out lines
  - family member present for reassurance and re-orientation
  - calendar, clock for orientation cues
- biological
  - low dose antipsychotics
  - haloperidol has the most evidence; reasonable alternatives include risperidone, olanzapine or quetiapine
  - benzodiazepines only to be used in alcohol withdrawal delirium; otherwise, can worsen delirium
- physical restraints if patient becomes violent

## Prognosis

- up to 50% 1 yr mortality rate after episode of delirium

## Dementia

- see [Neurology](#), N17

### DSM-IV-TR Diagnostic Criteria for Dementia (Alzheimer's Type)

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- the development of multiple cognitive deficits manifested by both
  - memory impairment (impaired ability to learn new information or to recall previously learned information)
  - $\geq 1$  of the following cognitive disturbances:
    - ♦ aphasia (language disturbance)
    - ♦ apraxia (impaired ability to carry out motor activities despite intact motor function)
    - ♦ agnosia (failure to recognize or identify objects despite intact sensory function)
    - ♦ disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting)
- the cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
- the course is characterized by gradual onset and continuing cognitive decline
- the cognitive deficits in Criteria A1 and A2 are not due to any of the following:
  - other central nervous system conditions that cause progressive deficits in memory and cognition
  - systemic conditions that are known to cause dementia
  - substance-induced conditions
- the deficits do not occur exclusively during the course of a delirium
- the disturbance is not better accounted for by another Axis I disorder

## Epidemiology

- prevalence increases with age: 10% in patients >65 yr of age; 25% in patients over 85 yr of age
- prevalence is increased in people with Down's syndrome and head trauma
- Alzheimer's dementia comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia – see [Neurology](#), N18)
- average duration of illness from onset of symptoms to death is 8-10 yr

## Subtypes

- with or without behavioural disturbance (e.g. wandering, agitation)
- early onset: age of onset <65 yr
- late onset: age of onset >65 yr

## Investigations (rule out reversible causes)

- standard: see *Delirium*, PS19
- as indicated: VDRL, HIV, SPECT, CT head in dementia
- indications for CT head: same as for delirium, plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 mo), dementia of relatively short duration (<2 yr), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/seizures)



### Most Common Types of Dementia

- Alzheimer's dementia
- Vascular dementia
- Lewy-Body dementia
- Fronto-temporal dementia



### The 4 As of Dementia ( $\geq 5$ )

Amnesia  
Aphasia  
Apraxia  
Agnosia



### Risk of Death with Atypical Antipsychotic Drug Treatment for Dementia

JAMA 2005;294:1934-1943

**Purpose:** To assess the evidence for increased mortality from atypical antipsychotic drug treatment for delusions, aggression and agitation in dementia.

**Study Characteristics:** Meta-analysis of 15 RCTs with 5110 patients.

**Participants:** Patients with Alzheimer's disease or dementia.

**Results:** Death occurred more often among patients randomized to drugs (118 [3.5%] vs. 40 [2.3%]). The odds ratio by meta-analysis was 1.54; 95% confidence interval [CI], 1.06-2.23;  $P=0.02$ . Sensitivity analyses did not show evidence for differential risks for individual drugs or diagnosis.

**Conclusions:** Atypical antipsychotic drugs may be associated with a small increased risk of death compared to placebo. This risk should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity, and the efficacy and safety of alternatives.

## Management

- see [Neurology](#), N20 for further management
- treat underlying medical problems and prevent others
- provide orientation cues for patient (e.g. clock, calendar)
- provide education and support for patient and family (e.g. day programs, respite care, support groups, home care)
- consider long-term care plan (nursing home) and power of attorney/living will
- inform Ministry of Transportation about patient's inability to drive safely
- consider pharmacological therapy
  - cholinesterase inhibitors [e.g. donepezil (Aricept®)] for mild to severe disease
  - NMDA receptor antagonist (e.g. memantine) for moderate to severe disease
  - low-dose neuroleptics (e.g. risperidone, quetiapine), antidepressants or trazodone if behavioural or emotional symptoms prominent – start low and go slow
  - reassess pharmacological therapy every 3 mo



**Table 4. Comparison of Dementia, Delirium and Pseudodementia of Depression**

	Dementia	Delirium	Pseudodementia of Depression
<b>Onset</b>	Gradual/step-wise decline	Acute (h-d)	Subacute
<b>Duration</b>	Months-years	Days-weeks	Variable
<b>Natural History</b>	Progressive Usually irreversible	Fluctuating, reversible High morbidity/mortality in very old	Recurrent Usually reversible
<b>Level of Consciousness</b>	Normal	Fluctuating (over 24 h)	Normal
<b>Attention</b>	Not initially affected	Decreased (wandering, easy distraction)	Difficulty concentrating
<b>Orientation</b>	Intact initially	Impaired (usually to time and place), fluctuates	Intact
<b>Behaviour</b>	Disinhibition, impairment in ADL/IADL, personality change, loss of social graces	Severe agitation/retardation	Importuning, self-harm/suicide
<b>Psychomotor</b>	Normal	Fluctuates between extremes	Slowing
<b>Sleep Wake Cycle</b>	Fragmented sleep at night	Reversed sleep wake cycle	Early morning awakening
<b>Mood and Affect</b>	Labile but not usually anxious	Anxious, irritable, fluctuating	Depressed, stable
<b>Cognition</b>	Decreased executive functioning, paucity of thought	Fluctuating preceded by mood changes	Fluctuating
<b>Memory Loss</b>	Recent, eventually remote	Marked recent	Recent
<b>Language</b>	Agnosia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia)	Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes	Not affected
<b>Delusions</b>	Compensatory	Nightmarish and poorly formed	Nihilistic, somatic
<b>Hallucinations</b>	Variable	Visual common	Less common, auditory predominates
<b>Quality of Hallucinations</b>	Vacuous/bland	Frightening/bizarre	Self-deprecatory
<b>Medical Status</b>	Variable	Acute illness, drug toxicity	R/O systemic illness, medications

## Substance-Related Disorders



### Epidemiology

- 47% of those with substance abuse have mental health problems
- 29% of those with a mental health disorder have a substance use disorder
- 47% of those with schizophrenia and 25% of those with an anxiety disorder have a substance use disorder

### Types of Substance Use Disorders

1. **substance abuse**: maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by  $\geq 1$  of the following occurring within a 12 mo period
  - recurrent use in situations in which it is physically hazardous (e.g. driving)
  - recurrent use resulting in failure to fulfill major role obligation
  - recurrent substance-related legal problems
  - continued use despite interference with social or interpersonal function



#### Substance Abuse

##### HELP

Hazardous  
Education/work/home consequences  
Legal problems  
Personal/social consequences



2. **substance dependence:** maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by  $\geq 3$  occurring at any time in the same 12 mo period
- tolerance (need for increased amount to achieve intoxication or diminished effect with same amount of substance)
  - withdrawal/use to avoid withdrawal
  - taken in larger amount or over longer period than intended
  - persistent desire or unsuccessful efforts to cut down
  - excessive time to procure, use substance, or recover from its effects
  - important interests/activities given up or reduced
  - continued use despite physical/psychological problem caused/exacerbated by substance
- **Note:** in DSM-5 "Substance Use Disorders" will take the place of distinguishing substance abuse from substance dependence

### Classification of Substances

Depressants	Alcohol, Opioids, Barbiturates, Benzodiazepines, GHB
Stimulants	Amphetamines, Methylphenidate, Cocaine
Hallucinogens	Cannabis, LSD, PCP, Ketamine, Psilocybin



#### Substance Dependence

##### MCAT

More drug needed to achieve intoxication  
Cutting down unsuccessful  
Activities given up or reduced  
Time to procure, use substance, or recover from effects is excessive

## Nicotine

- see [Family Medicine](#), *Smoking Cessation*, FM10



## Alcohol

- see [Family Medicine](#), *Alcohol*, FM12 and [Emergency Medicine](#), ER48



### History

- CAGE: validated screening questionnaire
  - C ever felt the need to Cut down on drinking?
  - A ever felt Annoyed at criticism of your drinking?
  - G ever feel Guilty about your drinking?
  - E ever need a drink first thing in morning (Eye opener)?
    - for men, a score of  $\geq 2$  is a positive screen; for women, a score of  $\geq 1$  is a positive screen
    - if positive CAGE, then assess further to distinguish between problem drinking and alcohol dependence



Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)

### General Assessment

- When was your last drink?
- Do you have to drink more to get the same effect?
- Do you get shaky or nauseous when you stop drinking?
- Have you ever had a withdrawal seizure?
- How much time and effort do you put into obtaining alcohol?
- Has your drinking affected your ability to work, go to school, or have relationships?
- Have you suffered any legal consequences?
- Has your drinking caused any medical problems?



#### A "Standard Drink"

Spirit (40%): 1.5 oz. or 43 mL  
Table Wine (12%): 5 oz. or 142 mL  
Fortified Wine (18%): 3 oz. or 85 mL  
Regular Beer (5%): 12 oz. or 341 mL

OR

1 pint of beer = 1.5 SD  
1 bottle of wine = 5 SD  
1 "mickey" = 8 SD  
"26-er" = 17 SD  
"40 oz." = 27 SD

**Table 5. Canada's Low-Risk Alcohol Drinking Guidelines**

Moderate Drinking		
Men: 3 or less/d ( $\leq 15$ /wk)	Women: 2 or less/d ( $\leq 10$ /wk)	Elderly: 1 or less/d

### Alcohol Intoxication

- legal limit for impaired driving is 10.6 mmol/L (50 mg/dL) reached by 2-3 drinks/h for men and 1-2 drinks/h for women
- coma can occur with  $>60$  mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)



### Alcohol Withdrawal

- occurs within 12 to 48 h after prolonged heavy drinking and can be life-threatening
- alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced
  - stage 1 (onset 12-18 h after last drink): "the shakes" tremor, sweating, agitation, anorexia, cramps, diarrhea, sleep disturbance
  - stage 2 (onset 7-38 h): alcohol withdrawal seizures, usually tonic-clonic, nonfocal and brief
  - stage 3 (onset 48 h): visual, auditory, olfactory or tactile hallucinations
  - stage 4 (onset 3-5 d): delirium tremens, confusion, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (fever, tachycardia, hypertension)
- course: in young almost completely reversible; elderly often left with cognitive deficits
- mortality rate 20% if untreated



#### Delirium Tremens

(alcohol withdrawal delirium)

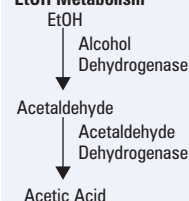
- Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)
- Hand tremor
- Insomnia
- Psychomotor agitation
- Anxiety
- Nausea or vomiting
- Tonic-clonic seizures
- Visual/tactile/auditory hallucinations
- Persecutory delusions

## Management of Alcohol Withdrawal

- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
  - areas of assessment include
    - nausea and vomiting
    - tactile disturbances
    - tremor
    - auditory disturbances
    - agitation
    - paroxysmal sweats
    - visual disturbances
    - anxiety
    - headache, fullness in head
    - orientation and clouding of sensorium
  - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67
    - mild <10
    - moderate 10-20
    - severe >20



### EtOH Metabolism



**Table 6. CIWA-A Scale Treatment Protocol for Alcohol Withdrawal**

<b>Basic Protocol</b>	Diazepam 20 mg PO q1-2h prn until CIWA-A <10 points Observe 1-2 h after last dose and re-assess on CIWA-A scale Thiamine 100 mg IM then 100 mg PO OD for 3 d Supportive care (hydration and nutrition)
<b>History of Withdrawal Seizures</b>	Diazepam 20 mg PO q1h for minimum of three doses regardless of subsequent CIWA scores
<b>If age &gt;65 or patient has severe liver disease, severe asthma or respiratory failure</b>	Use a short acting benzodiazepine Lorazepam PO/SL/IM 1-4 mg q1-2h
<b>If Hallucinations are present</b>	Haloperidol 2-5 mg IM/PO q1-4h – max 5 doses/d or atypical antipsychotics (olanzapine, risperidone) Diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold)
<b>Admit to Hospital if</b>	Still in withdrawal after >80 mg of diazepam Delirium tremens, recurrent arrhythmias, or multiple seizures Medically ill or unsafe to discharge home

## Wernicke-Korsakoff Syndrome

- alcohol-induced amnesic disorders due to thiamine deficiency
- necrotic lesions: mammillary bodies, thalamus, brainstem
- Wernicke's encephalopathy (acute and reversible): triad of nystagmus (CN VI palsy), ataxia and confusion
- Korsakoff's syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and confabulations; cannot occur during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal
- management
  - Wernicke's: thiamine 100 mg PO OD x 1-2 wk
  - Korsakoff's: thiamine 100 mg PO bid/tid x 3-12 mo

## Treatment of Alcohol Dependence

- non-pharmacological**
  - psychotherapy: motivational enhancement therapy (MET, increasing motivation to change), CBT (assertiveness training, increasing social support, planning leisure activities), marital and family therapy
  - behaviour therapy: contingency management, community reinforcement approach (CRA)
  - supportive services: counseling, detoxification centres, Alcoholics Anonymous
  - inpatient programs (e.g. 28-day programs)
    - individual readiness for change must always be considered with non-pharmacological interventions (refer to Prochaska's Stages of Change Model, [Population Health and Epidemiology](#), PH6)
- pharmacological**
  - naltrexone: opioid antagonist, shown to be successful in reducing the "high" associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges
  - disulfiram (Antabuse®): blocks oxidation of alcohol (blocks acetaldehyde dehydrogenase); with alcohol consumption, acetaldehyde accumulates to cause a toxic reaction (vomiting, tachycardia, death); if patient relapses, must wait 48 h before restarting Antabuse®
  - acamprosate (Campral): NMDA glutamate receptor antagonist; useful in maintaining abstinence and decreasing cravings



### Opioid Antagonists: Naltrexone vs. Naloxone

Naltrexone (Revia®)

- Used for opioid and EtOH dependence
- Long half life (h)

Naloxone (Narcan®):

- Used for life-threatening CNS/respiratory depression in opioid overdose
- Short half life (<1 h)
- Very fast acting (min)
- High affinity for opioid receptor
- Induces opioid withdrawal symptoms

## Opioids

- types of opioids: heroin, morphine, oxycodone, Tylenol #3® (codeine), hydromorphone
- major risks associated with the use of contaminated needles: increased risk of hepatitis B and C, bacterial endocarditis, HIV/AIDS

## Acute Intoxication

- direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), and respiratory depression

### Toxic Reaction

- typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
- management
  - ABCs
  - IV glucose
  - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
  - treatment: intubation and mechanical ventilation,  $\pm$  naloxone drip, until patient alert without naloxone (up to 48+ h with long-acting opioids)
- caution with longer half-life; may need to observe for toxic reaction for at least 24 h

### Withdrawal

- symptoms: depression, insomnia, drug-craving, myalgias, nausea, chills, autonomic instability (lacrimation, rhinorrhea, piloerection)
- onset: 6-12 h; duration: 5-10 d
- complications: loss of tolerance (overdose on relapse), miscarriage, premature labour
- management: long-acting oral opioids (methadone, buprenorphine),  $\alpha$ -adrenergic agonists (clonidine)

### Treatment of Chronic Abuse

- psychosocial treatment (e.g. Narcotics Anonymous) usually emphasize total abstinence
- naltrexone or naloxone (opioid antagonists) may also be used to extinguish drug-seeking behaviour
- long-term treatment may include withdrawal maintenance treatment with methadone or buprenorphine
- Suboxone® formulation includes naloxone in addition to buprenorphine, in an effort to prevent injection of the drug. When naloxone is injected, it will precipitate opiate withdrawal and block the opiate effect of buprenorphine, however it will not have this antagonist action when taken sublingually

**Table 7. Comparison of Methadone and Suboxone® (buprenorphine and naloxone)**

	Suboxone®	Methadone
<b>Mechanism of action</b>	Combined formulation of partial opiate agonist and opiate antagonist (which is only active when injected)	Full opiate agonist
<b>Ceiling effect</b>	Yes. This limits the risk of overdose and abuse potential	No. Higher risk of overdose and abuse potential
<b>Half life</b>	36-48 h, dosing can be daily or alternate days	24-36 h, daily dosing
<b>Withdrawal symptoms</b>	Mild	Moderate/severe
<b>Effectiveness</b>	Limited to mild/moderate opioid dependence	More effective for severe opioid dependence
<b>Cost</b>	Expensive	Inexpensive
<b>FDA approval</b>	2002	1947

## Cocaine

- street names: blow, C, coke, crack, flake, freebase, rock, snow
- alkaloid extracted from leaves of the coca plant; blocks presynaptic uptake of dopamine (causing euphoria), norepinephrine and epinephrine (causing vasospasm, hypertension)
- self-administered by inhalation or intravenous route

### Intoxication

- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (e.g. tachycardia, mydriasis, sweating)
- prolonged use may result in paranoia and psychosis

### Overdose

- medical emergency: hypertension, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias
- treatment with IV diazepam to control seizures and propranolol or labetalol to manage hypertension and arrhythmias

### Withdrawal

- initial "crash" (1-48 h): increased sleep, increased appetite
- withdrawal (1-10 wk): dysphoric mood plus fatigue, irritability, vivid unpleasant dreams, insomnia or hypersomnia, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management



#### Maintenance Medication for Opiate Addiction:

##### The Foundation of Recovery

*J Addict Dis* 2012;31:207-225

**Study:** Review.

**Discussion:** Maintenance treatment of opioid addiction with methadone or buprenorphine is associated with retention in treatment, reduction in illicit opiate use, decreased craving, and improved social function. Recently, studies showing extended release naltrexone injections have showed some promise.



#### OxyNEO vs. OxyContin

As of 2012, OxyContin was no longer available in Canada and was replaced by a new formulation of oxycodone called OxyNEO. OxyNEO is reported to be more tamper-resistant than OxyContin as the tablet is more difficult to crush. Furthermore, if OxyNEO is crushed, and added to water, it forms a thick gel-like substance that cannot be easily injected.



#### Common Presentations of Drug Use

System	Findings
<b>General</b>	Weight loss (especially cocaine, heroin) Injected conjunctiva (cannabis) Pinpoint pupils (opioids) Track marks (injection drugs)
<b>MSK</b>	Trauma
<b>GI</b>	Viral hepatitis (injection drugs) Unexplained elevations in ALT (injection drugs)
<b>Behavioural</b>	Missed appointments Non-compliance Drug-seeking (especially benzodiazepines, opioids)
<b>Psychological</b>	Insomnia Fatigue Depression Flat affect (benzodiazepines, barbiturates) Paranoia (cocaine) Psychosis (cocaine, cannabis, hallucinogens)
<b>Social</b>	Marital discord Family violence Work/school Absenteeism and poor performance

### Treatment of Chronic Abuse

- psychotherapy, group therapy, NA (narcotics anonymous) and behaviour modification useful in maintaining abstinence

### Complications

- cardiovascular: arrhythmias, MI, CVA, ruptured AAA
- neurologic: seizures
- psychiatric: psychosis, paranoia, delirium, suicidal ideation

## Amphetamines

- intoxication characterized by euphoria, improved concentration, sympathetic and behavioural hyperactivity and at high doses can cause coma
- chronic use can produce a paranoid psychosis which can resemble schizophrenia with agitation, paranoia, delusions and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- treatment of stimulant psychosis: antipsychotics

## Cannabis

- cannabis (marijuana) is the most commonly used illicit drug
- psychoactive substance: delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC)
- intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, altered sensorium, increased appetite, increased sense of well-being, euphoria/laughter, muscle relaxation, impaired performance on psychomotor tasks including driving
- high doses can cause depersonalization, paranoia, anxiety and may trigger psychosis and schizophrenia if predisposed
- chronic use associated with tolerance and an apathetic, amotivational state
- cessation does produce a significant withdrawal phenomenon
- treatment of dependence: behavioural and psychological interventions to maintain an abstinent state

## Hallucinogens

- types of hallucinogens: LSD, mescaline, psilocybin mushrooms, PCP, salvia
- LSD is a highly potent drug; intoxication characterized by tachycardia, HTN, mydriasis, tremor, hyperpyrexia, and a variety of perceptual and mood changes
- high doses can cause depersonalization, paranoia, and anxiety
- no specific withdrawal syndrome characterized
- treatment of agitation and psychosis: support, reassurance, diminished stimulation; benzodiazepines or high potency antipsychotics seldom required

## “Club Drugs”

Table 8. The Mechanism and Effects of Common “Club Drugs”

Drug	Mechanism	Effect	Adverse Effects
<b>MDMA</b> (“Ecstasy”, “X”, “E”)	Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and stimulant	Enhanced sensorium; feelings of well-being, empathy	Sweating, tachycardia fatigue, muscle spasms (especially jaw clenching), ataxia, hyperthermia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death
<b>Gamma Hydroxybutyrate</b> (GHB, “G”, “Liquid Ecstasy”)	Biphasic dopamine response (inhibition then release) and releases opiate-like substance	Euphoric effects, increased aggression, impaired judgment	Sweating, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, severe withdrawal from abrupt cessation of high doses: tremor, seizures, psychosis
<b>Flunitrazepam</b> (Rohypnol®, “Roofies”, “Rope”, “The Forget Pill”)	Potent benzodiazepine, rapid oral absorption	Sedation, psychomotor impairment, amnesic effects, decreased sexual inhibition	CNS depression with EtOH
<b>Ketamine</b> (“Special K”, “Kit-Kat”)	NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics and by veterinarians	“Dissociative” state, profound amnesia/analgesia; hallucinations and sympathomimetic effects	Psychological distress, accidents due to intensity of experience and lack of bodily control, in overdose, decreased LOC, respiratory depression, catatonia



### Medical Uses of Marijuana

- Anorexia-cachexia (AIDS, cancer)
- Spasticity, muscle spasms (multiple sclerosis, spinal cord injury)
- Levodopa-induced dyskinesia (Parkinson's Disease)
- Controlling tics and obsessive-compulsive behaviour (Tourette's syndrome)
- Reducing intra-ocular pressure (glaucoma)



### Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review

*The Lancet* 2007;370:319-328

**Purpose:** To review the evidence for cannabis use and occurrence of psychotic or affective mental health outcomes.

**Study Characteristics:** A meta-analysis of 35 population-based longitudinal studies, or case-control studies nested within longitudinal designs.

**Results:** There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio = 1.41, 95% CI 1.20-1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently (2.09, 95% CI, 1.54-2.84). Findings for depression, suicidal thoughts and anxiety outcomes were less consistent. In both cases (psychotic and affective outcomes) a substantial confounding effect was present.

**Conclusions:** The findings are consistent with the view that cannabis increases risk of psychotic outcomes independent of transient intoxication effects, although evidence is less strong for affective outcomes. Although cannabis use and the development of psychosis are strongly associated, it is difficult to determine causality and it is possible that the association results from confounding factors or bias. The authors did conclude that there is sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.



### Date Rape Drugs

- GHB
- Flunitrazepam (Rohypnol®)
- Ketamine



### Formication

Tactile hallucination that insects or snakes are crawling over or under the skin. Especially associated with crystal meth use.



### Pharm Party

An increasing trend among teenagers where assorted prescription medications are brought to a party and ingested at random.

**Table 8. The Mechanism and Effects of Common “Club Drugs” (continued)**

Drug	Mechanism	Effect	Adverse Effects
<b>Methamphetamine</b> ("speed", "meth", "chalk", "ice", "crystal")	Amphetamine stimulant, induces norepinephrine, dopamine and serotonin release	Rush begins in min, effects last 6-8 h, increased activity, decreased appetite, general sense of well-being, tolerance occurs quickly, users often binge and crash	Short term use: high agitation, rage, violent behaviour, occasionally hyperthermia and convulsions Long term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (esp. formication), delusions, mood disturbance, suicidal and homicidal thoughts, stroke, may be contaminated with lead, and IV users may present with acute lead poisoning
<b>Phencyclidine</b> ("PCP", "angel dust")	Not understood, used by veterinarians to immobilize large animals	Amnestic, euphoric, hallucinatory state	Horizontal/vertical nystagmus, myoclonus, ataxia, autonomic instability (treat with diazepam IV), prolonged agitated psychosis (treat with haloperidol); high risk for suicide; violence towards others High dose can cause coma

## Somatoform Disorders

### General Characteristics

- physical signs and symptoms lacking a known medical basis in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance
- cause significant distress or impairment in functioning
- symptoms are produced unconsciously and are not the result of malingering or factitious disorder
- primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict; no external incentive
- secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (e.g. work)

### Management of Somatoform Disorders

- brief frequent visits
- limit number of physicians involved in care
- focus on psychosocial not physical symptoms
- minimize medical investigations; coordinate necessary investigations
- psychotherapy: CBT, biofeedback, conflict resolution
- minimize psychotropic drugs: anxiolytics in short term only, antidepressants for depressive symptoms

- **Note:** significant changes in DSM-5



**Malingering:** intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external reward (e.g. avoiding work, obtaining financial compensation or obtaining drugs).

**Factitious disorder:** intentional production or feigning of physical or psychological signs or symptoms in order to assume the sick role where external incentives (e.g. economic gain) are absent.

## Body Dysmorphic Disorder

- preoccupation with imagined defect in appearance or excess concern around a slight anomaly
- usually related to the face
- M=F, prevalence 1-2.2% in the community; 6-15% in dermatology/cosmetic surgery clinics
- may lead to avoidance of work or social situations

## Conversion Disorder



- one or more symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or GMC (e.g. impaired co-ordination, local paralysis, double vision, seizures or convulsions)
- psychological factors thought to be etiologically related to the symptoms as the initiation of symptoms is preceded by conflicts or other stressors
- 11-300/100,000 in general population; focus of treatment in 1-3% of outpatient referrals to mental health clinics
- more common in rural populations and in individuals with little medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 mo)



## Hypochondriasis

- preoccupation with fear of having, or the idea that one has, a serious disease based on a misinterpretation of one or more bodily signs or symptoms
- evidence does not support diagnosis of a physical disorder
- fear of having a disease despite medical reassurance
- belief is not of delusional intensity (as in delusional disorder, somatic type) as person acknowledges unrealistic interpretation
- duration is  $\geq 6$  mo; onset in 3rd-4th decade of life
- community prevalence 1.1-4.5%; prevalence in general medical practice 4-9%; higher in psychiatric settings

## Pain Disorder

- pain is primary symptom and is of sufficient severity to warrant medical attention
- usually no organic pathology but when it exists, reaction is excessive
- lifetime prevalence 12%
- psychiatric disorders (mood, anxiety, substance) may precede, co-exist or result from pain disorder

## Somatization Disorder

- recurring, multiple, clinically significant physical complaints which result in patient seeking treatment or having impaired functioning
- $\geq 8$  physical symptoms that have no organic pathology including each of:
  - four pain symptoms related to at least four different sites or functions
  - two gastrointestinal symptoms, not including pain
  - one sexual symptom, not including pain
  - one pseudo-neurological symptom, not including pain (e.g. numbness, paresthesia)
- onset before age 30; extends over a period of years
- lifetime prevalence 0.2-2% among women and 0.2% among men
- cultural factors may influence sex ratio
- complications: anxiety, depression, unnecessary medications or surgery
- often a misdiagnosis for an insidious illness so rule out all organic illnesses (e.g. multiple sclerosis)

## Dissociative Disorders

### Definition

- dissociation so severe that the usually integrated functions of consciousness and perception of self break down
- sudden or gradual onset, transient or chronic course
- symptoms cause distress or impaired functioning
- differential diagnosis: PTSD, acute stress disorder, somatization disorder, substance abuse, GMC (e.g. complex/partial seizures)

**Table 9. Dissociative Disorders**

	Amnesia	Fugue	Identity Disorder	Depersonalization Disorder
<b>Diagnosis</b>	Inability to recall important personal information, usually of a traumatic or stressful nature; may be localized, selective or generalized	Sudden, unexpected travel away from home or workplace with inability to recall some or all of one's past; may assume new identity	Two or more distinct personalities that take control of an individual's behaviour; amnesia regarding personal history (aka Multiple Personality Disorder)	Persistent or recurrent experiences of feeling detached from one's mental processes or body (i.e. like being in a dream)
<b>Epidemiology</b>	6% prevalence Increased in survivors of trauma (war, abuse)	0.2% prevalence May occur under traumatic circumstances (combat, rape, natural disasters)	1.3% prevalence, M:F=1.3:9 May have history of physical or sexual abuse	Rare disorder Approximately 50% of adults have experienced a single brief episode of depersonalization, precipitated by extreme stress
<b>Treatment</b>	Psychotherapy, hypnosis No proven role for barbiturates/ pharmacologically-assisted interviewing	Usually spontaneous recovery Psychotherapy, hypnosis Ensure stability and safety No proven role for barbiturates/ pharmacologically-assisted interviewing	Three stages: symptom stabilization, attention to trauma, reintegration Psychotherapy, hypnosis Symptom-oriented adjuvants (antidepressants, anxiolytics) No proven role for barbiturates/ pharmacologically-assisted interviewing	Psychotherapy Pharmacotherapy: clonazepam, fluoxetine, clomipramine



## Sleep Disorders

- see [Neurology](#), N42



### Criteria for Diagnosis

- causes significant distress or impairment in functioning
- not due to medications, drugs, or a GMC

## Nocturnal Myoclonus

- middle-aged and elderly
- myoclonic jerks every 20-40 s
- bed partner complaints
- treatment: benzodiazepines (clonazepam, nitrazepam)

## Narcolepsy

- see [Neurology](#), N42



## Primary Insomnia

- see [Family Medicine](#), FM48



## Sleep Apnea

- see [Respirology](#), R31



## Sexuality and Gender



### Gender Dysphoria

- gender identity is set at approximately 3 yr of age
- **typical presentation**
  - strong and persistent cross-gender identification
  - repeated stated desire or insistence that one is of the opposite sex
  - preference for cross-dressing, cross-gender roles in make-believe play
  - intense desire to participate in the stereotypical games and pastimes of the opposite sex
  - strong preference for playmates of the opposite sex
  - significant distress or impairment in functioning and persistent discomfort with his or her sex or gender role
- **treatment**
  - psychotherapy
  - hormonal therapy
  - sexual reassignment surgery

## Paraphilias

- **definition:** recurrent, intense sexual arousal, fantasies, sexual urges or behaviour involving non-human objects, suffering or humiliation of oneself or one's partner, children or other non-consenting person causing significant distress or impairment in social, occupational or other areas of functioning
- **subtypes:** exhibitionism, fetishism, frotteurism, voyeurism, pedophilia, sexual masochism, sexual sadism, transvestite fetishism, paraphilia NOS
- rarely self-referred; come to medical attention through interpersonal or legal conflict
- person usually has more than one paraphilia; 5% of paraphilias attributed to women
- **typical presentation**
  - begins in childhood or early adolescence; increasing in complexity and stability with age
  - chronic, decreases with advancing age but may increase with stress
- **treatment**
  - anti-androgen drugs
  - behaviour modification
  - psychotherapy

### SEXUAL DYSFUNCTION

- see [Gynecology](#), GY31 and [Urology](#), U30



# Eating Disorders



## Epidemiology

- anorexia nervosa (AN): 1% of adolescent and young adult females; onset 13-20 yr old
- bulimia nervosa (BN): 2-4% of adolescent and young adult females; onset 16-18 yr old
- F:M=10:1; mortality 5-10%

## Etiology

- multifactorial: psychological, sociological and biological associations
- individual: perfectionism, lack of control in other life areas, history of sexual abuse
- personality: obsessive-compulsive, histrionic, borderline
- familial: maintenance of equilibrium in dysfunctional family
- cultural factors: prevalent in industrialized societies, idealization of thinness in the media
- genetic factors
  - AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs versus concordance in 1 of 14 dizygotic pairs
  - BN: higher familial incidence of affective disorders than the general population

## Risk Factors

- physical factors: obesity, chronic medical illness (e.g. diabetes mellitus)
- psychological factors: individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance abuse), history of sexual abuse, homosexual males, competitive athletes, concurrent associated mental illness [depression, OCD, anxiety disorder (especially panic and agoraphobia), substance abuse (specifically for BN)]

# Anorexia Nervosa

## DSM-IV-TR Diagnostic Criteria for Anorexia Nervosa

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected)
- intense fear of gaining weight or becoming fat, even though underweight
- disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight
- in postmenarcheal females, amenorrhea, i.e. the absence of at least three consecutive menstrual cycles (note: this criterion has been removed in DSM-5)

## Specific Type

- **restricting**: during the current episode of AN, the person has not regularly engaged in binge-eating or purging behaviour
- **binge-eating/purging**: during the current episode of AN, the person has regularly engaged in binge-eating or purging behavior

## Management

- outpatient programs and inpatient programs are available
- inpatient hospitalization for treatment of eating disorders is rarely on an acute basis (unless there is a concurrent psychiatric reason for emergent admission e.g. suicide risk)
- admit to a medical ward for hospitalization: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry or if actively suicidal
- agree on target body weight on admission and reassure this weight will not be surpassed
- psychotherapy (individual/group/family): addressing food and body perception, coping mechanisms, health effects
- monitor for complications of AN (see Table 10)
- monitor for refeeding syndrome:
  - a potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
  - complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium and death
  - prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, close monitoring of electrolytes and cardiac status



### Athletic Triad

- Disordered eating
- Amenorrhea
- Osteoporosis



### Screening Question for Purging Behaviours

"To lose weight, some people will use laxatives or vomit, have you ever tried that or used other ways to lose weight?"



Some diabetics may use insulin to lose weight, be aware of this in Type 1 DM.

### Prognosis

- early intervention much more effective
- with treatment, 70% resume a weight of at least 85% of expected levels and about 50% resume normal menstrual function
- eating peculiarities and associated psychiatric symptoms are common and persistent
- long-term mortality: 10% to 20% of patients hospitalized will die in next 10 to 30 yr (secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion committing suicide)

## Bulimia Nervosa

### DSM-IV-TR Diagnostic Criteria for Bulimia Nervosa

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition, (Copyright 2000). American Psychiatric Association.

- recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following
  1. eating, in a discrete period of time, an amount of food that is larger than most people would eat during a similar period of time and under similar circumstances
  2. a sense of lack of control over eating during the episode (e.g. a feeling that one cannot stop eating or control what or how much one is eating)
- recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise
- the binge eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for 3 mo
- self-evaluation is unduly influenced by body shape and weight
- the disturbance does not occur exclusively during episodes of AN



#### Ipecac Syrup

- Was commonly used to induce vomiting in accidental poisoning or drug overdose
- Used chronically by some patients with EDs to induce vomiting

### Specific Type

- **purging:** during the current episode of BN, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
- **non-purging:** during the current episode of BM, the person has used other inappropriate compensatory behaviours, such as fasting or excessive exercise, but has not regularly engaged in purging behaviours

### Associated Features

- fatigue and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
- tooth decay
- swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention
- reddened knuckles, Russell's sign (knuckle callus from self-induced vomiting)
- trouble concentrating
- weight fluctuation over time

### Management

- admission for significant electrolyte abnormalities
- biological: treatment of starvation effects, SSRIs
- psychological: develop trusting relationship with therapist to explore personal etiology and triggers, CBT, family therapy, recognition of health risks
- social: challenge destructive societal views of women, use of hospital environment to provide external patterning for normative eating behaviour

### Prognosis

- few recover without recurrence
- good prognostic factors: onset before age 15, achieving a healthy weight within 2 yr of treatment
- poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance

**Table 10. Physiologic Complications of Eating Disorders**

System	Starvation/Restriction	Binge-Purge
General	Low BP, low HR, significant orthostatic changes ± syncopal episodes, low temperature, vitamin deficiencies	Russell's sign (knuckle callus) Parotid gland enlargement Perioral skin irritation Periocular and palatal petechiae Loss of dental enamel and caries Aspiration pneumonia Metabolic alkalosis secondary to hypokalemia and loss of acid
Endocrine	Primary or secondary amenorrhea, decreased $T_3/T_4$	
Neurologic	Grand mal seizure (decreased $Ca^{2+}$ , $Mg^{2+}$ , $PO_4^{3-}$ )	

**Table 10. Physiologic Complications of Eating Disorders** (continued)

System	Starvation/Restriction	Binge-Purge
<b>Cutaneous</b>	Dry skin, lanugo hair, hair loss or thinning, brittle nails, yellow skin from high carotene	
<b>GI</b>	Constipation, GERD, delayed gastric emptying	Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear
<b>CVS</b>	Arrhythmias, CHF	Arrhythmias, cardiomyopathy (from use of ipecac), sudden cardiac death (decreased K <sup>+</sup> )
<b>MSK</b>	Osteoporosis secondary to hypogonadism	Muscle wasting
<b>Renal</b>	Pre-renal failure (hypovolemia), renal calculi	Renal failure (electrolyte disturbances)
<b>Extremities</b>	Pedal edema (decreased albumin)	Pedal edema (decreased albumin)
<b>Lab Values</b>	Starvation: decreased RBCs, decreased WBCs, decreased LH, decreased FSH, decreased estrogen, decreased testosterone, increased growth hormone, increased cholesterol Dehydration: increased BUN	Vomiting: decreased Na <sup>+</sup> , decreased K <sup>+</sup> , decreased Cl <sup>-</sup> , decreased H <sup>+</sup> , increased amylase; hypokalemia with metabolic alkalosis Laxatives: decreased Na <sup>+</sup> , decreased K <sup>+</sup> , decreased Cl <sup>-</sup> , increased H <sup>+</sup> ; metabolic acidosis

**Borderline Personality Disorder****DESPAIRER**

Disturbance of identity  
Emotionally labile  
Suicidal behavior  
Paranoia or dissociation  
Abandonment (fear of)  
Impulsive  
Relationships unstable  
Emptiness (feelings of)  
Rage (inappropriate)

\*Created by Jason Caplan, MD

**Antisocial Personality Disorder****CORRUPT**

Cannot conform to law  
Obligations ignored  
Reckless disregard for safety  
Remorselessness  
Underhanded (deceitful)  
Planning insufficient (impulsive)  
Temper (irritable and aggressive)

## Personality Disorders

**General Diagnostic Criteria**

- an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual's culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- causes distress or impaired functioning not necessarily for the person with the personality disorder (PD), but for those around him/her
- pattern is stable and well established by adolescence or early adulthood
- associated with many complications, such as depression, suicide, violence, brief psychotic episodes, multiple drug use and treatment resistance
- each PD is present in 1% of the population and are lifelong and chronic
- the mainstay of treatment is psychotherapy with the addition of pharmacotherapy to treat associated axis I disorders (i.e. depression, anxiety, substance abuse)
- main treatment for borderline personality disorder is dialectical behavioural therapy (consists of validating rather than blaming the patient, and replacing maladaptive behaviour with adaptive behaviour)

**Table 11. Classification and Diagnosis of Personality Disorders**

**Note:** For each personality disorder, the most recognizable feature is indicated in *italics*

Diagnostic Cluster	Diagnosis
<b>Cluster A "Mad"</b> Patients seem odd, eccentric, withdrawn Familial association with psychotic disorders Common defense mechanisms: intellectualization, projection, magical thinking	<b>Paranoid Personality Disorder (0.5-3%)*</b> <i>Pervasive distrust and suspiciousness of others, interpret motives as malevolent</i> Blame problems on others and seem angry and hostile Diagnosis requires 4 of: 1. Suspicious that others are exploiting or deceiving them 2. Pre-occupied with trustworthiness of acquaintances 3. Reluctant to confide in others 4. Interpret benign remarks as threatening, demeaning 5. Holds grudges 6. Perceives attacks on character and is quick to counterattack 7. Questions fidelity of partner without justification
	<b>Schizotypal Personality Disorder (3-5.6%)</b> <i>Pattern of eccentric behaviours, peculiar thought patterns</i> Diagnosis requires 5 of: 1. Ideas of reference 2. Odd beliefs, magical thinking (inconsistent with cultural norms e.g. belief in telepathy, superstitions) 3. Unusual perceptual experiences (e.g. bodily illusions) 4. Suspiciousness 5. Inappropriate or restricted affect 6. Odd, eccentric appearance or behaviour (e.g. involved in cults, strange religious practices) 7. Few close friends 8. Odd thinking, odd speech (e.g. vague, stereotyped) 9. Excessive social anxiety
	<b>Schizoid Personality Disorder*</b> <i>Neither desires nor enjoys close relationships including being a part of a family; prefers to be alone.</i> <i>Lifelong pattern of social withdrawal</i> <i>Seen as eccentric and reclusive with restricted affect</i> Diagnosis requires 4 of: 1. Does not enjoy or desire close relationships 2. Chooses solitary activities 3. Little to no interest in sexual activity with others 4. Takes pleasure in few (if any) activities 5. Few or no close friends 6. Indifference to praise or criticism 7. Emotionally cold, detached, or has flattened affect

**Table 11. Classification and Diagnosis of Personality Disorders** (continued)

Diagnostic Cluster	Diagnosis	
<b>Cluster B “Bad”</b> Patients seem dramatic, emotional, inconsistent Familial association with mood disorders Common defense mechanisms: denial, acting out, regression (histrionic PD), splitting (borderline PD), projective identification, idealization/devaluation	<b>Borderline Personality Disorder (2-4%)</b> <i>Unstable moods and behaviour, feel alone in the world, problems with self image</i> <i>History of repeated suicide attempts, self-harm behaviours</i> <i>**10% suicide rate**</i> Diagnosis requires 5 of: 1. Frantic efforts to avoid real or imagined abandonment 2. Unstable and intense relationships 3. Unstable sense of self 4. Impulsivity in two potentially harmful ways (sexual, drugs, spending) 5. Recurrent suicidal behaviour/self-harm 6. Unstable mood/affect 7. General feelings of emptiness 8. Difficulty controlling anger 9. Transient dissociative symptoms or paranoid ideation associated with stress	<b>Narcissistic Personality Disorder (2%)</b> <i>Sense of superiority, needs constant admiration, lacks empathy, but with fragile sense of self</i> <i>Consider themselves “special” and will exploit others for personal gain</i> Diagnosis requires 5 of: 1. Exaggerated sense of self-importance (grandiosity) 2. Preoccupied with fantasies of unlimited success, power, beauty, love 3. Believes he/she is “special” and should associate with other “special” people 4. Requires excessive admiration 5. Sense of entitlement 6. Takes advantage of others 7. Lacks empathy 8. Envious of others or believes that others are envious of him/her 9. Arrogant attitudes
	<b>Antisocial Personality Disorder (M: 3%, F: 1%)</b> <i>Lack of remorse for actions, manipulative and deceitful, often violate the law. May appear charming on first impression</i> <i>Pattern of disregard for others and violation of rights of others must be present before the age of 15, however, for the diagnosis of ASPD patients must be at least 18</i> Diagnosis requires 3 of the following: 1. Failure to conform to social norms by committing unlawful acts 2. Deceitfulness, lying, manipulating others for personal gain 3. Impulsive, fails to plan ahead 4. Irritable, aggressive, repeated fights or assaults 5. Recklessness and disregard for personal safety, safety of others 6. Irresponsible, cannot sustain work 7. Lack of remorse for actions	<b>Histrionic Personality Disorder (1.3-3%)*</b> <i>Attention-seeking behaviour and excessively emotional. Are dramatic, flamboyant and extroverted. Cannot form meaningful relationships. Often sexually inappropriate</i> Diagnosis requires 5 of: 1. Not comfortable unless centre of attention 2. Inappropriately sexually seductive 3. Uses physical appearance to attract attention 4. Speech is impressionistic, lacks detail 5. Theatrical and exaggerated expression of emotion 6. Easily influenced by others 7. Perceives relationships as more intimate than they actually are
<b>Cluster C “Sad”</b> Patients seem anxious, fearful Familial association with anxiety disorder Common defense mechanisms: isolation, avoidance, hypochondriasis	<b>Avoidant Personality Disorder (0.5-1.6%)</b> <i>Timid and socially awkward with a pervasive sense of inadequacy and fear of criticism</i> <i>Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited</i> Diagnosis requires 4 of: 1. Avoids occupational activities that involve significant interpersonal contact for fear of criticism or rejection 2. Unwilling to get involved with people unless certain of being liked 3. Restrained in intimate relationships for fear of being shamed or ridiculed 4. Preoccupied with being rejected or criticized in social situations 5. Inhibited in new interpersonal situations due to fear of inadequacy 6. Views him or herself as inferior, socially inept or personally unappealing 7. Reluctant to engage in new activities for fear of embarrassment	<b>Obsessive-Compulsive Personality Disorder (3-10%)</b> <i>Preoccupation with orderliness, perfectionism, and mental and interpersonal control</i> <i>Is inflexible, closed-off, and inefficient</i> Diagnosis requires 4 of: 1. Preoccupation with details, rules, lists, order, organization, or schedules to the extent that the point of an activity is lost 2. Perfectionism interferes with task completion 3. Excessively devoted to work to the exclusion of leisure activities and friendships 4. Inflexible about morality/ethics/values 5. Unable to discard worthless objects of no sentimental value 6. Reluctant to delegate tasks to others 7. Miserly spending style (money is hoarded for future disasters) 8. Rigid and stubborn
	<b>Dependent Personality Disorder (1.6-6.7%)*</b> <i>Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviours</i> <i>Difficulty making everyday decisions</i> Diagnosis requires 5 of: 1. Difficulty making everyday decisions without advice and reassurance from others 2. Needs others to assume responsibility for most major areas of his/her life 3. Difficulty expressing disagreement 4. Difficulty initiating projects due to lack of self-confidence 5. Goes to excessive lengths to obtain support 6. Uncomfortable or helpless when alone because of fear of being unable to take care of him/herself 7. Urgently seeks another relationship as a source of care and support when a close relationship ends 8. Unrealistically preoccupied with fears of being left to take care of him/herself	

**OCPD vs. OCD**

	OCPD	OCD
<b>Ego-syntonic or ego-dystonic</b>	Ego-syntonic	Ego-dystonic
<b>Thought content</b>	Obsessional thinking, no compulsions, strict routine and rigidity in day-to-day matters	Obsessions and compulsions, rituals

\*DSM-V HAS PROPOSED CHANGES TO THESE PERSONALITY DISORDERS



Table 12. Key Differences between Schizoid, Schizotypal and Schizophrenia

	Schizoid	Schizotypal	Schizophrenia
<b>Thought form</b>	Organized	Organized, but vague and circumstantial	Disorganized, tangential, loosening of associations
<b>Thought content</b>	No psychosis	No psychosis, may have ideas of reference, paranoid ideation, odd beliefs and magical thinking	Psychosis, hallucinations
<b>Relationships</b>	Solitary, NO desire for social relationships	Lacks close relationships, INTERESTED in relationships but socially inept	Socially marginalized, but not by choice



### Obsessive-Compulsive Personality Disorder

#### SCRIMPER

Stubborn  
Cannot discard worthless objects  
Rule obsessed  
Inflexible  
Miserly  
Perfectionistic  
Excludes leisure due to devotion to work  
Reluctant to delegate to others

\*Created by Jason Caplan, MD



### Dependent Personality Disorder

#### RELiance

Reassurance required  
Expressing disagreement difficult  
Life responsibilities assumed by others  
Initiating projects difficult  
Alone (feels helpless and uncomfortable when alone)  
Nurturance (goes to excessive lengths to obtain)  
Companionship sought urgently  
Exaggerated fears of being left to care for self



Consider speaking to children alone.  
Always consider child abuse. See [Pediatrics](#), P14.



### Tips for the Child Interview:

- Use language the child will understand (i.e. don't ask about feeling of worthlessness, ask about whether they feel like they're a bad kid)
- Children in some cultures are taught to be quiet and avoid eye contact with adults who are authority figures (do not mistake with depression)
- Use developmentally-appropriate questions (i.e. don't ask about lack of interest in activities, ask children whether they feel bored)



### HEADSSS Interview

Home environment  
Education/Employment  
Activities  
Drugs/Diet  
Sex  
Safety  
Suicide/depression



Attachment type can be assessed in infants 10-18 mo of age using the Strange Situation test, in which the child is stressed by the caregiver being removed from the situation and the stranger staying. Attachment style is measured by the child's behaviour during the reunion with the caregiver.



Attachment problems may present as a child who is difficult to soothe, has difficulty sleeping, problems feeding, tantrums or behaviours.

## Child Psychiatry

### The Child Psychiatric Interview

- **ID**
  - name, age, school grade, living situation, family situation (all family members, age and occupation of parents), demographics
- **Chief Complaint**
  - onset, time course, stressors, impact on child's and family's functioning, supports
  - child's functioning and behaviour at home, at school, and with peers
  - mental status (see MSE, PS3)
- **History of Present Illness**
  - symptoms and features of most likely diagnostic area [e.g. disruptive behaviour disorders (ADHD, CD, ODD), developmental disorders, learning disorders, abuse, mood disorders, and anxiety disorders]
  - in adolescents, consider psychotic disorders, eating disorders, and substance abuse disorders
  - screen for comorbid conditions
  - what was the child like before and after the symptoms? what has changed? what is happening now?
- **Additional History**
  - past history: pregnancy, neonatal, developmental, temperamental, medical, surgical
  - psych history: past assessments (e.g. psychiatric, psychological, educational), treatments
  - family history: similar symptoms, medical, developmental, and psychosocial issues
- **Risk Assessment**
  - physical/sexual abuse, suicidality, aggression/homicidality, firesetting, risky behaviour
  - past risk issues (past suicide attempts, past aggression), previous contact with child protection services
  - brief developmental history: pregnancy, birth, milestones, general behaviour, parents' method of discipline, school functioning, peer relationships

### Developmental Concepts

- **temperament**: innate psycho-physiological and behavioural characteristics of a child (e.g. emotionality, activity, and sociability); spectrum from "difficult" to "slow-to-warm-up" to "easy temperament", plotted on nine parameters:
  - activity level, adaptation, attention span and persistence, distractibility, intensity of reaction, quality of mood, response to a new stimulus, rhythmicity, threshold of responsiveness
- **parental fit**: the congruence between parenting style (authoritative, authoritarian, permissive) and child's temperament
- **attachment**: special relationship between child and primary caretaker(s); develops during first year, best predictor of a child's attachment style is their parent's attachment style (see Table 13)
- **stranger anxiety** (8 mo): infants cry at approach of stranger
- **separation anxiety** (10-18 mo): separation from attachment figure results in distress

Table 13. Attachment Models

Parent/Caregiver	Attachment Type	Features in Child
Loving, consistently available, sensitive, and receptive	Secure	Able to use caregiver to calm self
Rejecting, unavailable psychologically, insensitive responses	Insecure (avoidant)	Not reliant on caregiver for soothing
Inconsistent, insensitive responses, role reversal	Insecure (ambivalent/resistant)	
Frightening, dissociated, sexualized, or atypical	Disorganized	



## Mood Disorders

### MAJOR DEPRESSIVE DISORDER (MDD)

#### Epidemiology

- pre-pubertal 1-2% (no gender differences); post-pubertal 4-18% (F:M = 2:1)

#### Clinical Presentation

- see *Adult Mood Disorders*, PS9
- physical factors: insomnia (children), hypersomnia (adolescents), somatic complaints, substance abuse
- psychological factors: irritability, boredom, anhedonia, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation
- comorbid diagnoses of anxiety, ADHD, conduct disorder, and eating disorders

#### Treatment

- majority never seek treatment
- individual (CBT, IPT)/family therapy and education, modified school program
- SSRIs (strongest evidence for fluoxetine)
- ECT: only in adolescents
- light therapy, self-help books

#### Prognosis

- prolonged episodes, up to 1-2 yr
- adolescent onset predicts chronic mood disorder; up to 2/3 will have another depressive episode within 5 yr
- complications
  - negative impact on family and peer relationships
  - school failure
  - significantly increased risk of suicide attempt (10%) or completion
  - substance abuse



Irritable mood is a diagnostic feature unique to children and adolescents.

### BIPOLAR DISORDER

#### Clinical Presentation

- see *Adult Bipolar Disorder/Mania*, PS12
- mixed presentation and psychotic symptoms (hallucinations and delusions) more common in adolescent population than adult population
- unipolar depression may be an early sign of adult bipolar disorder
  - ~30% of psychotic depressed adolescents receive a bipolar diagnosis within 2 yr of presentation
  - associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family, pharmacologically induced mania

#### Treatment

- 1st line: mood stabilizers and/or antipsychotics
- 2nd line: antidepressants, benzodiazepines (careful of disinhibiting effect)



- Health Canada advises Canadians under the age of 18 to consult physicians if they are being treated with SSRIs, SNRIs or mirtazapine. This request was made as a result of international reports that some of these drugs may be associated with an increased risk of suicidal ideation in patients under the age of 18. There was no increased risk of suicide completion
- FDA advises that the use of SSRIs in youth <24 yr old associated with increased suicidal ideation. No studies show association to completed suicide



**Fluoxetine, Cognitive-Behavioral Therapy and Their Combination for Adolescents with Depression: Treatment for Adolescents with Depression Study (TADS) Randomized Controlled Trial**

JAMA 2004;292:807-820

**Study:** Randomized controlled trial at 13 US academic and community clinics between spring 2000-summer 2003.

**Patients:** 439 patients ages 12-17 with a primary DSM IV diagnosis of major depressive disorder.

**Outcomes:** Children's Depression Rating Scale-Revised (CDRSR) total score.

**Interventions:** 12 wk of (1) fluoxetine (10-40 mg/d), (2) CBT, (3) CBT + fluoxetine (10-40 mg/d), or (4) placebo.

**Results:** Fluoxetine with CBT had a statistically significant CDRSR score as compared to placebo ( $P=0.001$ ) with a 71% response rate. This combo was greater than fluoxetine alone ( $P=0.02$ ), and CBT alone ( $P=0.01$ ). Fluoxetine alone was greater than CBT alone ( $P=0.01$ ).

## Anxiety Disorders

- prevalence 2-15%; F:M = 2:1

#### Diagnosis

- school problems, recurrent physical symptoms (abdominal pain, headaches) especially in mornings, social and relationship problems, social withdrawal and isolation, family conflict, irritability and mood symptoms, alcohol and drug use in adolescent

#### Treatment

- family psychotherapy, predictive and supportive environment
- CBT: child and parental education, relaxation techniques (e.g. deep breathing), exposure/desensitization, recognizing and correcting anxious thoughts
- pharmacotherapy: SSRIs (e.g. fluoxetine), benzodiazepines (e.g. clonazepam – use with caution, may have disinhibiting effect)
  - fluvoxamine and sertraline also have good evidence, particularly for OCD

## SEPARATION ANXIETY DISORDER

### Epidemiology

- prevalence: 4% of children/adolescents
- on average 7.5 yr old at onset, 10 yr old at presentation
- common for mother to have an anxiety or depressive disorder

### Differential Diagnosis

- simple or social phobia, depression, learning disorder, truancy, conduct disorder, school-related problems (e.g. bullying)

### Clinical Presentation

- excessive and developmentally inappropriate anxiety on separation from primary caregiver with physical or emotional distress for at least 4 wk
- school refusal (75%)
- persistent worry, refusal to sleep, clinging, nightmares, somatic symptoms
- comorbid major depression common (2/3)
- worry about something happening to parent or themselves if separated

### Prognosis

- if inadequately treated early on, may present later in a more severe form
- may develop into panic disorder with/without agoraphobia

## SOCIAL PHOBIA (SOCIAL ANXIETY DISORDER)

- must distinguish between shy child and child with social anxiety
  - diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning, or if markedly distressed
- features: temper tantrums, freezing, clinging behaviour, mutism, excessively timid, stays on periphery, refuses to be involved in group play
- must be capable of developing social relationships
- must occur in settings with peers, not just adults
- selective mutism:
  - does not speak in front of others; no problems speaking at home
  - must rule out language or communication problems
  - severe form of social anxiety

## POST-TRAUMATIC STRESS DISORDER

- diagnostic criteria same as adults (see *PTSD*, PS17)
  - in children, reliving of the trauma may occur through repetitive play which simulates the event, nightmares of the trauma which may progress to generalized nightmares (e.g. monsters), psychosomatic symptoms, omen formation (belief that there were predictors of the trauma which can be avoided in the future to escape future trauma)
- common examples include: sexual/physical abuse, witnessing family violence, natural disasters
- can also be associated with onset of sexual activity

## OBSESSIVE-COMPULSIVE DISORDER

- diagnostic criteria same as adults, except it is not necessary for child to recognize thoughts or actions as excessive or unreasonable (see *OCD*, PS16)
- 0.3-1% of children/adolescents; tends to begin earlier in boys than girls
  - tend to engage in rituals at home rather than in front of others
  - associated with Tourette's disorder, tics, and ADHD
  - small subset associated with Group A Strep infections; has prepubertal onset and neurologic symptoms

## PANIC DISORDER

- diagnostic criteria same as adults (see *Panic Disorder*, PS14)
- genetic/parental modeling/identification hypothesized as cause
- often parent with panic or depressive disorder

## GENERALIZED ANXIETY DISORDER

- diagnostic criteria same as adults (see *GAD*, PS15)
  - **Note:** Only 1 item is required in children for Criteria C
- often redo tasks, show dissatisfaction with their work and tend to be perfectionistic
- often require reassurance and support to take on new tasks

## SPECIFIC PHOBIA

- common phobias in childhood include a fear of heights, small animals, doctors, dentists, darkness, loud noises, thunder and lightning



### Newer Generation Antidepressants for Depressive Disorders in Children and Adolescents

*Cochrane DB Syst Rev* 2012;11:CD004851

**Study:** Meta-analysis of 19 trials containing 3335 participants (including RCTs, cross-over trials and cluster trials).

**Population:** Children and adolescents aged 6-18 yr with diagnosed depressive disorder.

**Interventions:** Antidepressants, placebo.

**Main Outcome Measure:** Depression severity score.

**Results:** Children treated with an antidepressant had lower depression severity score and higher rates of response/remission. Children on antidepressants were also found to be at increased risk (58%) of suicide-related outcome (RR 1.58; 95% CI 1.02 to 2.45).

**Conclusions:** In children and adolescents, antidepressants are effective at treating depression, yet may cause a higher chance of suicide-related outcomes.



The shy child is quiet and reluctant to participate but slowly 'warms up'.

## Childhood Schizophrenia

### Epidemiology

- 1/2,000 in childhood; increases after puberty to adult rates (1%) in late adolescence
- diagnostic criteria same as in adults (see *Schizophrenia*, PS6)
- less elaborate delusions than adults and visual hallucinations are more common
- <6 yr old may present in similar fashion to autism prior to onset of core symptoms
- prognosis poor as cognitive, language, social and personality development are disrupted

### Treatment

- psychotherapy, family education
- low dose antipsychotics for psychotic symptoms (e.g. hallucinations) and target behaviours (e.g. aggression, hyperactivity, impulsiveness)
- hospitalization or residential placement, if severe



Disorganized speech and behaviour is associated with many childhood disorders which must be differentiated from schizophrenia (e.g. Communication Disorders, Pervasive Developmental Disorders, ADHD, Stereotypic Movement Disorders)

## Pervasive Developmental Disorders

- include autism, Asperger's, childhood disintegrative disorder, Rett's disorder, and PDD NOS
- M:F = 3-4:1 (except for Rett's with female predominance)

### Differential Diagnosis

- developmental disability, childhood schizophrenia, social phobia, OCD, communication disorder, non-verbal learning disorder, ADHD, abuse, hearing or visual impairment, seizure disorder, motor impairment

### Management

- hearing test to rule out impairment
- psychological testing to assess intellectual functioning and learning
- chromosomal analysis to rule out abnormalities (e.g. trisomy 21, fragile X syndrome)
- rule out psychotic disorders, social problems, depression, anxiety, abuse

### Treatment

- team-based: school, psychologist, occupational therapist, physiotherapist, speech and language therapy, audiology, pediatrics, psychiatry
- family education and support
- treat concomitant disorders such as tics, OCD, anxiety, depression, and seizure disorder
- behaviour management, school programming
- pharmacotherapy: atypical antipsychotics (for aggression, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated inattention and hyperactivity)

### Prognosis

- variable, but improves with early intervention
- better if IQ >60 and able to communicate
- **Note:** DSM-V has resulted in significant changes to these diagnoses. Autism, Asperger's disorder, childhood disintegrative disorder and PDD NOS will be subsumed by the diagnosis of autism spectrum disorder

## AUTISTIC DISORDER

- prevalence 1/1,000
- abnormalities in three areas:
  - **social interaction:** impaired non-verbal behaviours (eye contact, facial expression, hand gestures); failure to develop appropriate peer relationships; lack of seeking to share enjoyment/interests; lack of social/emotional reciprocity
  - **communication:** delay or lack of development of spoken language; impaired ability to start or sustain conversation with others; stereotyped/repetitive or idiosyncratic use of language; lack of make-believe play
  - **restricted and repetitive behaviours, interests, and activities:** stereotyped or restricted patterns of interest with abnormal intensity or focus; inflexible adherence to specific, non-functional routines; stereotyped hand or body movements (e.g. rocking); preoccupation with parts of objects (e.g. spinning wheels on toy cars only)
- at least 6 features before 3 yr old (at least 2 from social interaction and 1 from other 2 categories)

## ASPERGER'S DISORDER

- prevalence 3/1,000
- no early speech and language delay, no cognitive deficits (express normal curiosity in environment and develop age-appropriate learning skills, self-help and adaptive behaviours), normal to high intelligence
- at least 2 items from social interaction and 1 from repetitive behaviours categories of autistic disorder criteria



### Asperger's vs. Autism

Children with Asperger's have no delay or abnormality in language or cognition. Autism must have age of onset by 3 years whereas Asperger's may not be diagnosed until later in life.

## CHILDHOOD DISINTEGRATIVE DISORDER (CDD)

- similar to autism, but there must be a period of at least 2 yr (and up to 10 yr) of normal development followed by regression in multiple areas of functioning
- associated with developmental disability
- rule out degenerative brain disease, schizophrenia, general medical conditions

## RETT'S DISORDER

- X-linked dominant disorder, therefore predominantly in girls
- restriction of brain growth beginning in first year of life
- normal development between 6 mo to 4 yr, then regression (loss of purposeful hand movements, developmental disability, seizures, neurological, respiratory and motor deficits)



	Rett's	CDD
<b>Development</b>	Normal development and head size until ≥5 mo	Normal development for ≥2 yr
<b>Incidence</b>	6-7/100,000 females	1/100,000 boys > girls
<b>Deficits</b>	Decreased head growth, hand movements, skills (social, coordination, language)	Decreased skills (language, social, motor), bowel/bladder control, play



### Observe child for "ATTENTION" features

Annoying  
Temperamental  
Energetic  
Noisy  
Task incompletion  
Inattentive  
Oppositional  
Negativism



### A Systematic Review and Analysis of Long-term Outcomes in Attention Deficit Hyperactivity Disorder: Effects of Treatment and Non-treatment

*BMC Med* 2012;10:99

**Study:** Systematic review of 351 studies.

**Purpose:** To determine the long-term outcomes of ADHD and whether there is an effect on long-term outcomes with treatment.

**Population:** Patients with diagnosed or symptomatic presentation of ADHD.

**Interventions:** No treatment (control), Treatment (pharmacological, non-pharmacological and multi-modal).

**Outcome Groups:** Drug use/addictive behavior, academic outcomes, antisocial behavior, social function, occupation, self-esteem, driving outcomes, services use, obesity.

**Results:** Untreated participants with ADHD had poorer outcomes vs. non-ADHD participants in 74% (n=244) of studies, while 26% (n=89) showed similar outcomes. 72% (n=37) of studies showed a benefit from ADHD treatment vs. untreated ADHD and 28% (n=15) showed no benefit. Treatment of ADHD was found to be beneficial in studies looking at driving (100%), obesity (100%), self-esteem (90%), social function (83%), academic outcomes (71%), drug use/addictive behavior (67%), antisocial behavior (50%) and occupation (33%).

**Conclusions:** Overall, people with ADHD have poorer long-term outcomes than controls (those without ADHD). For those with ADHD, treatment improves long-term outcomes.

## Attention Deficit Hyperactivity Disorder

- prevalence: 5-12% of school-aged children; M:F = 4:1, although girls may be under-diagnosed
- girls tend to have inattentive/distractible symptoms; boys have impulsive/hyperactive symptoms

### Etiology

- genetic: dopamine candidate genes, catecholamine/neuroanatomical hypothesis
- cognitive: developmental disability, inhibitory control and other errors of executive function
- arousal: alterations in the sensory system filters

### Diagnosis

- differential: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (fetal alcohol syndrome, Fragile X), lead poisoning, history of head injury, traumatic life events (abuse)
- diagnosis (3 subtypes):
  - **Combined Type:** 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity-impulsivity
  - **Predominantly Inattentive Type:** 6 or more symptoms of inattention
  - **Predominantly Hyperactive-Impulsive Type:** 6 or more symptoms of hyperactivity-impulsivity
  - symptoms persist for >6 mo
  - onset before age 7
  - symptoms present in at least two settings (i.e. home, school, work)
  - interferes with academic, family, and social functioning
  - does not occur exclusively during the course of another psychiatric disorder

**Table 14. Core Symptoms of ADHD (DSM-IV)**

Inattention	Hyperactivity	Impulsivity
Careless mistakes	Fidgets, squirms in seat	Blurts out answers before questions completed
Cannot sustain attention in tasks or play	Leaves seat when expected to remain seated	Difficulty awaiting turn
Does not listen when spoken to directly	Runs and climbs excessively	Interrupts/intrudes on others
Fails to complete tasks	Cannot play quietly	
Disorganized	On the "go", driven by a motor	
Avoids, dislikes tasks that require sustained mental effort	Talks excessively	
Loses things necessary for tasks or activities		
Distractible		
Forgetful		

### Features

- average onset 3 yr old
- identification upon school entry
- rule out developmental delay, genetic syndromes, encephalopathies or toxins (alcohol, lead)
- risk of substance abuse, particularly cannabis and cocaine, depression, anxiety, academic failure, poor social skills, risk of comorbid CD and/or ODD, risk of adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics

### Treatment

- non-pharmacological: parent management, anger control strategies, positive reinforcement, social skills training, individual/family therapy, resource room, tutors, classroom intervention, exercise routines, extracurricular activities
- pharmacological
  - standard treatment:
    - ♦ stimulants: methylphenidates [Ritalin<sup>®</sup>, Concerta<sup>®</sup> (long-acting)], Bupropion<sup>®</sup>
    - ♦ amphetamines: dextroamphetamine, mixed amphetamine salts (Adderall<sup>®</sup>), lisdexamfetamine (Vyvanse<sup>®</sup>)
    - ♦ SNRI: atomoxetine (Strattera<sup>®</sup>)
  - for comorbid symptoms: antidepressants, antipsychotics

### Prognosis

- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable
- 70-80% continue into adolescence, but hyperactive symptoms usually abate

## Oppositional Defiant Disorder

- prevalence: 2-16%

### Diagnosis

- pattern of negativistic/hostile and defiant behaviour for  $\geq 6$  mo with  $\geq 4$  of:
  - loses temper, argues with adults, defies adult rules, deliberately annoys, blames others, touchy/easily annoyed, angry and resentful, spiteful or vindictive
- behaviour causes significant impairment in social, academic or occupational functioning
- behaviours do not occur exclusively during the course of a psychotic or mood disorder
- criteria not met for conduct disorder (CD); if 18 yr or older, criteria not met for ASPD
- features that typically differentiate ODD from transient developmental stage: onset  $< 8$  yr, chronic duration ( $> 6$  mo), frequent intrusive behaviour
- impact of ODD: poor school performance, few friends, strained parent/child relationships
- may progress to CD

### Treatment

- establish boundaries
- parent management training and psychoeducation
- individual/family therapy
- pharmacotherapy for comorbid disorders
- school/day care interventions to help with behaviour management



#### ODD kids "ARE BRATS"

Annoying  
Resentful  
Easily annoyed  
Blames others  
Rule breaker  
Argues with adults  
Temper  
Spiteful/vindictive

## Conduct Disorder

- prevalence: 1.5-3.4% (M:F = 4-12:1)

### Etiology

- parental/familial factors: parental psychopathology (e.g. ASPD, substance abuse), child rearing practices (e.g. child abuse, discipline), low socio-economic status (SES), family violence
- child factors: difficult temperament, ODD, learning problems, neurobiology

### Diagnosis

- differential: ADHD, depression, head injury, substance abuse
- diagnosis: use multiple sources (Achenbach Child Behavioural Checklist, Teacher's Report Form)
  - pattern of behaviour that violates rights of others and age appropriate social norms with  $\geq 3$  criteria noted in past 12 mo and  $\geq 1$  in past 6 mo:
    - ♦ aggression to people and animals (bullying, physical fights, use of weapons, forced sex)
    - ♦ destruction of property, firesetting with intent to damage
    - ♦ deceitfulness or theft (breaking and entering, car theft)
    - ♦ violation of rules (out all night before age 13, runaway  $\geq 2$  times or for long periods of time, often truant from school before age 13)
  - disturbance causes clinically significant impairment in social, academic or occupational functioning
  - if individual is 18 yr or older, criteria not met for ASPD
- diagnostic types
  - childhood onset: at least one criterion prior to age 10
    - ♦ poor prognosis: associated with ODD, aggressiveness, impulsiveness
  - adolescent onset: absence of any criteria until age 10
    - ♦ better prognosis; least aggressive, gang-related delinquency
  - mild, moderate, severe



#### Conduct Disorder Diagnosis

##### TRAP

Theft: breaking and entering, deceiving, non-confrontational stealing  
Rule breaking: running away, skipping school, out late  
Aggression: people, animals, weapons, forced sex  
Property destruction

## Treatment

- early intervention necessary and more effective; long-term follow-up required
- parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training, medications for aggressiveness or comorbid disorders
- pharmacotherapy is insufficient; mainly used for treatment of comorbid disorders

## Prognosis

- poor prognostic indicators include early-age onset, high frequency and variety of behaviours, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance abuse
- 50% of CD children become adult ASPD

- see [Pediatrics](#):

- *Child Abuse*, [Pediatrics](#) P14
- *Chronic Recurrent Abdominal Pain*, [Pediatrics](#) P39
- *Developmental Delay*, [Pediatrics](#) P22
- *Intellectual Disability*, [Pediatrics](#) P23
- *Learning Disability*, [Pediatrics](#) P25
- *Elimination Disorders*, [Pediatrics](#) P9
- *Sleep Disturbances*, [Pediatrics](#) P12



- see [Neurology](#):

- *Tic Disorders*, [Neurology](#), N28
- *Tourette's Syndrome*, [Neurology](#), N28



## Psychotherapy

- theory: one's present outlook is shaped by one's past and unconscious psychological forces
- insight allows change in personality and behaviour
- conflict – three stages
  - non-resolvable conflict
  - attempt to repress
  - return of conflict in disguised form (symptom or character trait)
- emphasis on early interaction with caregiver
- sources of information
  - past and present experiences and relationships
  - relationship with therapist
    - ♦ **transference**: unconscious reenactment of early interpersonal patterns in relationship with therapist
    - ♦ **countertransference**: therapist's transference to patient
    - ♦ **resistance**: elements in the patient which oppose treatment
- techniques
  - free association: patient says whatever comes to mind
  - dream analysis
- Prochaska's stages of change model is important for all conflict resolutions

## Defense Mechanisms

- defense mechanisms are unconsciously activated by the patient in response to anxiety provoking events and feelings

**Table 15. Defense Mechanisms**

<b>Level 1: Psychotic Defenses</b> Common in psychosis; normally seen throughout childhood and in dreams	
	<ul style="list-style-type: none"> <li>• <b>Denial</b>: replacing external reality with wishful fantasy</li> <li>• <b>Distortion</b>: reshaping of reality to meet inner beliefs</li> <li>• <b>Projection</b>: interpreting internal impulses as though they are outside oneself; in psychosis seen as frank delusion about reality (e.g. persecutory delusions)</li> </ul>
<b>Level 2: Immature Defenses</b> Common in personality disorders, severe depression. Normally seen throughout adolescence	
	<ul style="list-style-type: none"> <li>• <b>Acting out</b>: express unconscious wish through impulsive action</li> <li>• <b>Blocking</b>: of thinking, affect, or impulse</li> <li>• <b>Hypochondriasis</b>: exaggeration of illness</li> <li>• <b>Introjection</b>: internalizing qualities of an object (i.e. victim identifying with aggressor)</li> <li>• <b>Passive-aggressive behaviour</b></li> <li>• <b>Regression</b>: returning to an earlier stage of development to avoid present stressors</li> <li>• <b>Somatization</b>: unconscious expression of psychic pain/tension as physical symptoms</li> </ul>



**Table 15. Defense Mechanisms** (continued)

<b>Level 3: Neurotic Defenses</b> Common in adults	<ul style="list-style-type: none"> <li>• <b>Controlling</b></li> <li>• <b>Displacement:</b> shifting emotional response to an object/idea resembling that which is anxiety provoking</li> <li>• <b>Externalization:</b> attributing moods/attitudes/conflicts to external world or objects</li> <li>• <b>Inhibition:</b> limiting function to avoid anxiety producing internal conflicts</li> <li>• <b>Intellectualization:</b> using intellectual processing to avoid experiencing affect</li> <li>• <b>Isolation</b></li> <li>• <b>Rationalization:</b> using rational explanations to justify behaviours that are unacceptable</li> <li>• <b>Dissociation:</b> temporary modification of sense of self to avoid emotional distress</li> <li>• <b>Reaction formation:</b> transforming an unacceptable impulse into its opposite</li> <li>• <b>Repression:</b> withholding or removing from consciousness an idea/feeling</li> <li>• <b>Sexualization</b></li> </ul>
<b>Level 4: Mature Defenses</b> Common in emotionally healthy adults	<ul style="list-style-type: none"> <li>• <b>Altruism</b></li> <li>• <b>Anticipation:</b> planning for future discomfort</li> <li>• <b>Asceticism:</b> denying pleasurable effects of an experience</li> <li>• <b>Humour</b></li> <li>• <b>Suppression:</b> postpone attention to impulse or conflict</li> </ul>

## Psychodynamic Therapy

- **psychoanalysis** (exploratory psychotherapy)
  - original therapy developed by Freud, goal is self-revelation and insight
  - the exploration of the meaning of early experiences and how they affect emotions and patterns of behaviour presently
  - time intensive (e.g. 4-5 times/wk for 3-7 yr)
  - for individuals who can tolerate ambiguity in explorations of feelings and treatment
- **supportive psychotherapy**
  - goal is not insight but reduction of anxiety
  - strengthen healthy defense mechanisms to assist day-to-day functioning
  - techniques include: enhancing self-esteem, clarification, confrontation, rationalization, reframing, encouragement, rehearsal/anticipation, de-catastrophizing, allowing “venting” of frustrations
- **short term/brief psychotherapy**
  - resolution of particular emotional problems, or acute crisis
  - number of sessions agreed on at outset (6-20)
- **interpersonal psychotherapy**
  - short-term treatment looking at relationship patterns and teaching coping mechanisms
  - focus on personal social roles and relationships to help deal with problems in current functioning

## Behaviour Therapy

- modification of internal or external events which precipitate or maintain emotional distress; useful in the treatment of anxiety disorders, substance abuse, paraphilias
- **systematic desensitization:** mastering anxiety-provoking situations by approaching them gradually and in a relaxed state that limits anxiety
- **flooding:** confronting feared stimulus for prolonged periods until it is no longer frightening
- **positive reinforcement:** strengthening behaviour and causing it to occur more frequently by rewarding it
- **negative reinforcement:** causing behaviour to occur more frequently by removing a noxious stimulus when desired behaviour occurs
- **extinction:** causing a behaviour to diminish by not rewarding it
- **punishment** (aversion therapy): causing a behaviour to diminish by applying a noxious stimulus

## Cognitive Therapy

- theory: moods/emotions are influenced by one's thoughts
- psychiatric disturbances are frequently caused by habitual errors in thinking
- goal is to help patient become aware of inaccurate automatic thoughts and correct assumptions with a more balanced perspective
- useful for depression, anxiety disorders, self-esteem problems
- use of this therapy presupposes a significant level of functioning of the patient
- patients asked to keep thought records (often in chart form, with column headings “situation”, “feeling”, “thought” and “cognitive distortion”) to monitor their thoughts, when/where they think these thoughts, how the thoughts make them feel and what their underlying error in thinking might be

## Cognitive Behavioural Therapy (CBT)

- combines cognitive and behaviour therapies to teach the patient to weaken connections between thinking patterns, habitual behaviours and mood/anxiety problems
- good for treatment of mild/moderate depression/anxiety

## Dialectical Behavioural Therapy (DBT)

- therapy that combines CBT techniques with approaches derived from Buddhist meditation practices
- originally developed for borderline patients but has since been found to be effective for the treatment of several other disorders
- focuses on four types of skills: mindfulness, emotion regulation, interpersonal effectiveness, and distress tolerance
- individual and group therapy settings

## Other Therapies

- **group psychotherapy**
  - goals: self-understanding, acceptance, social skills
- **family therapy**
  - family system considered more influential than individual especially for children
  - focus on here and now, re-establishing parental authority, strengthening normal boundaries, and rearranging alliances
- **hypnosis**: mixed evidence for the treatment of pain, phobias, anxiety, and smoking cessation
- **mindfulness-based cognitive therapy**: derived from Buddhist meditative practices; aims to help people attend to thoughts, behaviours and emotions non-judgmentally and in the moment using guided breathing exercises

## Pharmacotherapy

### Antipsychotics

- “antipsychotics” and “neuroleptics” are terms used interchangeably
- **indications**: schizophrenia and other psychotic disorders, mood disorders with or without psychosis, violent behaviour, autism, Tourette’s, somatoform disorders, dementia, OCD
- **onset**: immediate calming effect and decrease in agitation; thought disorder responds in 2-4 wk
- **rational use**:
  - no reason to combine antipsychotics
  - choosing an antipsychotic:
    - ♦ all antipsychotics are equally effective, except for clozapine
    - ♦ atypical antipsychotics are as effective as typical or first generation antipsychotics but are thought to have better side effect profiles
    - ♦ choose a drug that the patient has responded to in the past or that was used successfully in a family member
  - route: PO, short-acting or long-acting depot IM injections, sublingual
  - duration: minimum 6 mo, usually for life

#### Long-Acting Preparations

- antipsychotics formulated in oil for IM injection (see Table 17)
- received on an outpatient basis
- indications: individuals with schizophrenia or other chronic psychosis who relapse because of non-adherence
- dosing: start at low dosages, and then titrate every 2 to 4 wk to maximize safety and minimize side effects
- should be exposed to oral form prior to first injection
- side effects: risk of EPS, parkinsonism, increased risk of neuroleptic malignant syndrome

#### Canadian Guidelines for the Treatment of Acute Psychosis in the Emergency Setting

- haloperidol 5 mg IM ± lorazepam 2 mg IM
- olanzapine 2.5-10 mg (PO, IM, quick dissolve)
- risperidone 2 mg (M-tab, liquid)



#### Two-year Randomized Controlled Trial and Follow-up of Dialectical Behaviour Therapy vs. Therapy by Experts for Suicidal Behaviours and Borderline Personality Disorder

*Arch Gen Psychiatry* 2006;63:757-66

**Objective:** To determine how DBT compares with non-behavioural psychotherapy.

**Study:** One-year randomized controlled trial followed by one year follow-up period.

**Patients:** 100 women with recent suicidal and self-injurious behaviours meeting DSM criteria and matched to various demographic data.

**Intervention:** One year of DBT or one year of non-behavioural therapy.

**Outcomes:** Trimester assessments of suicidal behaviour, emergency services use, general psychological well-being.

**Results:** Patients receiving DBT were half as likely to attempt suicide, required less hospitalization for suicidal ideation, had lower medical risk for suicide attempts, were less likely to drop out of therapy and had fewer emergency room visits for suicidal ideation.

**Conclusions:** DBT is effective in reducing suicidal behaviour in patients with borderline personality disorder.



#### Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

*NEJM* 2005;353:1209-23

**Study:** Randomized, double-blind, active-control trial with median follow-up of 6 mo.

**Patients:** 1432 patients with a diagnosis of schizophrenia (as per DSM-IV criteria) and able to take antipsychotic medications (as determined by study doctors). Mean age 41, 74% male, 26% female.

**Intervention:** 1 to 4 capsules daily of olanzapine (20.1 mg), quetiapine (543.4 mg), risperidone (3.9 mg), perphenazine (20.8 mg), or ziprasidone (112.8 mg), with dosage at the discretion of the study doctor. Mean modal doses in parentheses.

**Main Outcome:** Discontinuation of treatment for any cause

**Results:** Olanzapine group had statistically significant lower rate of discontinuation for any cause (64%) from all others (quetiapine – 82%, risperidone – 74%, perphenazine – 75%, ziprasidone – 79%). There were no significant differences in time until discontinuation due to intolerable side effects, however, olanzapine was associated with a significantly higher rate of metabolic side effects.

**Table 16. Pathophysiology of Schizophrenia vs. Mechanism of Action of Antipsychotics**

Brain Region	Pathophysiology in Schizophrenia	Typical Antipsychotic	Atypical Antipsychotic
<b>Limbic System</b>	Excess DA +ve symptoms (hallucinations, delusions)	D2 blockade Treats +ve symptoms	Weak 5-HT block, D2/1 blockade maintained Treats +ve symptoms
<b>Frontal Cortex</b>	Decreased DA -ve symptoms (flat affect, anhedonia, avolition), cognitive impairment	D2 blockade May worsen -ve symptoms and cognitive impairment	Robust 5-HT block increases DA transmission Theoretical improvement in negative/cognitive symptoms only observed with clozapine
<b>Basal Ganglia</b>	Unchanged	D2 blockade Relative ACh excess causes EPS symptoms	Robust 5-HT block increases DA transmission Decreased EPS incidence
<b>Tuberoinfundibular Tract</b>	Unchanged	D2 blockade Hyperprolactinemia	5-HT block increases DA Less hyperprolactinemia

DA = dopamine; 5-HT = serotonin; ACh = acetylcholine; EPS = extrapyramidal symptoms

Note: specific "typical" and "atypical" antipsychotics vary in terms of binding to adrenergic, 5-HT, cholinergic and histaminergic sites leading to different side effect profiles

**Table 17. Common Antipsychotic Agents**

	Starting Dose	Maintenance	Maximum	Relative Potency (mg)
<b>Typicals</b> (In order of potency from high to low)				
Haloperidol (Haldol®)	2-5 mg IM q4-8h 0.5-5 mg PO b/tid 0.2 mg/kg/d PO	Based on clinical effect	20 mg/d PO	2
Fluphenazine enanthate (Moditen®, Modecate® for IM formulation)	2.5-10 mg/d PO	1-5 mg PO qhs 25 mg IM/SC q1-3wk	20 mg/d PO	2
Zuclopenthixol HCl (Clopixol®)	20-30 mg/d PO	20-40 mg/d PO	100 mg/d PO	4
Zuclopenthixol acetate (Acuphase®)	50-150 mg IM q48-72h		400 mg IM (q2wk)	
Zuclopenthixol decanoate (Clopixol Depot®)	100 mg IM q1-4wk	150-300 mg IM q2wk	600 mg IM/wk	
Perphenazine (Trilafon®)	8-16 mg PO b/tid	4-8 mg PO t/qid	64 mg/d PO	10
Loxapine HCl (Loxitane®)	10 mg PO tid 12.5-50 mg IM q4-6h	60-100 mg/d PO	250 mg/d PO	10
Chlorpromazine (Largactil®)	10-15 mg PO b/t/qid	400 mg/d PO	1000 mg/d PO	100
<b>Atypicals</b> (in order of potency from high to low)				
Risperidone (Risperdal®, Risperdal Consta® for IM long acting preparation, Risperdal M-Tab for melting form – placed on tongue)	1-2 mg OD/bid	4-8 mg/d PO 25 mg IM q2wk	8 mg/d PO	2
Paliperidone (Invega®)	3 mg/d PO	3-12 mg/d PO	12 mg/d PO	4
Olanzapine (Zyprexa®, Zyprexa Zydys® for melting form – placed on tongue, Zyprexa Intramuscular®)	5 mg/d PO	10-20 mg/d PO	30 mg/d PO	5
Asenapine (Saphris®)	5 mg SL bid	5-10 mg SL bid	10 mg bid	5
Ziprasidone (Zeldox®)	20 mg bid PO	40-80 mg bid PO	160 mg/d PO	6
Aripiprazole (Ablify®)	10-15 mg/d PO	10-15 mg/d PO	30 mg/d PO	7.5
Quetiapine (Seroquel®, Seroquel XR for extended release®)	25 mg PO bid	400-800 mg/d PO	800 mg/d PO	75
Clozapine (Clozaril®)	25 mg PO bid	300-600 mg/d PO	600 mg/d PO	100

**Typical vs. Atypical Antipsychotics**

	Typical	Atypical
<b>Pros</b>	Inexpensive Plenty of injectible forms available	Fewer EPS Low risk of tardive syndromes Mood stabilizing
<b>Cons</b>	More EPS Tardive syndromes in long term Not mood stabilizing	Expensive Few injectible forms available Metabolic side effects (weight gain, hyperglycemia, lipid abnormalities, metabolic syndrome) Exacerbation (or new onset) of obsessive behaviour

Table 18. Commonly Used Atypical Antipsychotics

	Risperidone (Risperdal®)	Olanzapine (Zyprexa®, Zydys®)	Quetiapine (Seroquel®)	Clozapine (Clozaril®)	Aripiprazole (Abilify®)
<b>Mechanism</b>	Blocks 5-HT <sub>2</sub> , D2 and adrenergic receptors	Blocks 5-HT <sub>2,3,6</sub> , D1-D4, muscarinic, adrenergic, histaminergic receptors	Blocks 5-HT <sub>2A</sub> , D1-2, adrenergic and histaminergic receptors	Blocks 5-HT <sub>2,3</sub> , D1-4, muscarinic, histaminergic receptors	Partial agonist of D2, D3 and 5-HT <sub>1A</sub> receptors Antagonist of 5-HT <sub>2A</sub> receptors
<b>Advantages</b>	Low incidence of EPS at lower doses (< 8 mg)	Better overall efficacy compared to haloperidol Well tolerated Low incidence of EPS and TD	Associated with less weight gain compared to clozapine and olanzapine	Most effective for treatment-resistant schizophrenia Does not worsen tardive symptoms; may treat them Approximately 50% of patients benefit, especially paranoid patients and those with onset after 20 yr	Less weight gain and risk of metabolic syndrome compared to olanzapine and a lower incidence of EPS compared to haloperidol
<b>Disadvantages</b>	SE: insomnia, agitation, EPS, H/A, anxiety, prolactin, postural hypotension, constipation, dizziness, weight gain	SE: mild sedation, insomnia, dizziness, minimal anticholinergic, early AST and ALT elevation, restlessness Weight gain associated with increased risk of diabetes mellitus and hyperlipidemia	SE: H/A, sedation, dizziness, constipation Most sedating of first line atypicals	SE: drowsiness/sedation, hypersalivation, tachycardia, dizziness, EPS, NMS 1% agranulocytosis	SE: H/A, agitation, anxiety, insomnia, weight gain, decreased serum prolactin levels
<b>Comments</b>	Quick dissolve (M-tabs), and long-acting (Consta®) formulations available	Quick dissolve formulation (Zydys®) used commonly in ER setting for better compliance IM form available		Weekly blood counts for at least 1 mo, then q2wk Do not use with drugs which may cause bone marrow suppression due to risk of agranulocytosis	

Note: Risk of weight gain: Clozapine > Olanzapine > Quetiapine > Risperidone

Table 19. Side Effects of Antipsychotics

System	Side Effects
<b>Anticholinergic</b>	Dry mouth, urinary retention, constipation, blurred vision, toxic-confusional states
<b>α-adrenergic blockade</b>	Orthostatic hypotension, impotence, failure to ejaculate
<b>Dopaminergic blockade</b>	Extrapyramidal syndromes (dystonia, akathisia, pseudoparkinsonism, dyskinesia), galactorrhea, amenorrhea, impotence, weight gain
<b>Anti-histamine</b>	Sedation
<b>Hematologic</b>	Agranulocytosis (clozapine)
<b>Hypersensitivity reactions</b>	Liver dysfunction, blood dyscrasias, skin rashes, neuroleptic malignant syndrome, altered temperature regulation (hypothermia or hyperthermia)
<b>Endocrine</b>	Metabolic syndrome (see sidebar on PS42)

### Neuroleptic Malignant Syndrome (NMS)

- **psychiatric emergency**
- due to massive dopamine blockade; increased incidence with high potency and depot neuroleptics
- **risk factors**
  - medication factors
    - ♦ sudden increase in dosage, or starting a new drug
  - patient factors
    - ♦ medical illness
    - ♦ dehydration
    - ♦ exhaustion
    - ♦ poor nutrition
    - ♦ external heat load
    - ♦ sex: male
    - ♦ age: young adults



#### Commonly Used Atypical Antipsychotics

##### ROCS

Risperidone  
Olanzapine  
Clozapine  
Seroquel (quetiapine)



#### Anticholinergic Effects

**Red** as a beet  
**Hot** as a hare  
**Dry** as a bone  
**Blind** as a bat  
**Mad** as a hatter



#### Metabolic and Cardiovascular Adverse Effects Associated with Antipsychotic Drugs

*Nat Rev Endocrinol* 2012;8:114-126

**Study:** Review.

**Conclusions:** All antipsychotics can cause cardiovascular and metabolic side effects, such as obesity, dyslipidemia, hyperglycemia and metabolic syndrome. Olanzapine and clozapine are most likely to cause these side effects. The mechanism that underlies the metabolic and cardiovascular effects is not fully understood, however, the histamine, dopamine, serotonin and muscarinic receptors are implicated.

### • clinical presentation

- mental status changes (usually occur first), fever, autonomic reactivity, rigidity
- develops over 24-72 h
- labs: increased creatine phosphokinase, leukocytosis, myoglobinuria

### • treatment: discontinue drug, hydration, cooling blankets, dantrolene (hydrantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)

### • mortality: 5%

### Extrapyramidal Symptoms (EPS)

- incidence related to increased dose and potency
- acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)

**Table 20 Extrapyramidal Symptoms**

	Dystonia	Akathisia	Pseudoparkinsonism	Dyskinesia
<b>Acute or Tardive</b>	Both	Both	Acute	Tardive
<b>Risk Group</b>	Acute: Young Asian and Black males	Elderly females	Elderly females	
<b>Presentation</b>	Sustained abnormal posture; torsions, twisting, contraction of muscle groups; muscle spasms (e.g. oculogyric crisis, laryngospasm, torticollis)	Motor restlessness; crawling sensation in legs relieved by walking; very distressing, increased risk of suicide and poor adherence	Tremor; rigidity (cogwheeling); akinesia; postural instability (decreased/absent arm-swing, stooped posture, shuffling gait, difficulty pivoting)	Purposeless, constant movements, involving facial and mouth musculature, or less commonly – the limbs
<b>Onset</b>	Acute: within 5 d Tardive: >90 d	Acute: within 10 d Tardive: >90 d	Acute: within 30 d	Tardive: >90 d
<b>Treatment</b>	Acute: benztropine or diphenhydramine	Acute: lorazepam, propranolol or diphenhydramine; reduce or change neuroleptic to lower potency	Acute: benztropine (or benzodiazepine if side effects); reduce or change neuroleptic to lower potency	Tardive: no good treatment; may try clozapine; discontinue drug or reduce dose

### Antiparkinsonian Agents (Anticholinergic Agents)

- types
  - benztropine (Cogentin®) 2 mg PO, IM or IV OD (~1-6 mg)
  - amantadine (Symmetrel®) 100 mg PO bid (100-400 mg)
  - diphenhydramine (Benadryl®) 25-50 mg PO/IM qid
- do not always prescribe with neuroleptics
  - give only if at high risk for acute EPS or if acute EPS develops
- do not give these for tardive syndromes because they worsen the condition



### Features of Neuroleptic Malignant Syndrome

#### FARM

##### Fever

Autonomic changes (e.g. increased HR/BP, sweating)

##### Rigidity of muscles

Mental status changes (e.g. confusion)

FARM symptoms are also seen in Serotonin Syndrome (SS).

SS can be distinguished from NMS by the following:

SS	NMS
Twitchy, shivering, restless	Severe global rigidity
Flushed, sweaty	Pallor
Vomiting, diarrhea, abdominal pain	No GI symptoms



**Tardive Dyskinesia** may include grimacing, tongue protrusion, lip smacking, and rapid eye movement.

## Antidepressants

- onset of effect
  - relief of neurovegetative symptoms: 1-3 wk
  - relief of emotional/cognitive symptoms: 2-6 wk
- may use mild stimulant (e.g. methylphenidate) for severe neurovegetative symptoms briefly and taper down as antidepressant effect increases
- taper TCAs slowly (over weeks-months) because they can cause withdrawal reactions
- tapering of any kind of antidepressant may be required based on the half-life of the medication and the patient's individual sensitivity
- it is important to be particularly vigilant over the first 2 wk of therapy as neurovegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be particularly at risk for suicidal behaviour during this time)
- treatment of bipolar depression:
  - monotherapy with antidepressants is not advisable as a switch from depression to mania can occur
  - patients with bipolar disorder should only be treated with an antidepressant if it is combined with a mood stabilizer and antipsychotic
  - for patients taking mood stabilizers or antipsychotics, consider adding or switching to lithium or lamotrigine, or adding an SSRI or bupropion



### Selective Serotonin Reuptake Inhibitors (SSRIs) versus Other Antidepressants for Depression

Cochrane DB Syst Rev 2004; Issue 3

This systematic review of 98 RCTs compared the efficacy of SSRIs with other kinds of antidepressants in the treatment of patients with depressive disorders.

**Conclusions:** There is no significant difference in the effectiveness of SSRIs versus TCAs. Consider relative patient acceptability, toxicity and cost when choosing.

Table 21. Common Antidepressants

Class	Drug	Daily Starting Dose (mg)	Therapeutic Dose (mg)
SSRI	fluoxetine (Prozac®)	20	20-80
	fluvoxamine (Luvox®)	50-100	150-300
	paroxetine (Paxil®)	10	20-60
	sertraline (Zoloft®)	50	50-200
	citalopram (Celexa®)	20	20-40
	escitalopram (Cipralex®)	10	10-20
SNRI	venlafaxine (Effexor®)	37.5-75	75-225
	duloxetine (Cymbalta®)	40	40-60
NDRI	bupropion (Wellbutrin®)	100	300-450
TCA (3° Amines)	amitriptyline (Elavil®)	75-100	150-300
	imipramine (Tofranil®)	75-100	150-300
TCA (2° Amines)	nortriptyline (Aventyl®)	75-100	75-150
	desipramine (Norpramin®)	100-200	150-300
MAOI	phenelzine (Nardil®)	45	60-90
	tranylcypromine (Parnate®)	30	10-60
RIMA	moclobemide (Manerix®)	300	300-600
NASSA	mirtazapine (Remeron®)	15	15-45

(SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin and norepinephrine reuptake inhibitors; NDRI=norepinephrine and dopamine reuptake inhibitors; TCA=tricyclic antidepressants; MAOI= monoamine oxidase inhibitors; RIMA=reversible inhibition of MAO-A; NASSA=noradrenergic and specific serotonin antagonists)



#### Tips On Choosing Antidepressants

- All SSRIs have similar effectiveness, but consider side effect profiles and half-lives
- Bupropion causes less sexual dysfunction, weight gain, and sedation but is contraindicated for patients with history of seizure, stroke, brain tumour, brain surgery or closed head injury. Also used to treat eating disorders. Not recommended for anxiety because of stimulating effects
- Mirtazapine useful if insomnia or agitation are prominent, or to treat depression with cachexia
- Trazodone mainly used as adjunct for SSRI-induced sleep disturbances
- Sertraline, citalopram, and escitalopram have the least interactions with other drugs and are sleep-wake neutral
- Fluoxetine and paroxetine are the most activating drugs and should be taken in the morning
- Fluvoxamine is always sedating and should be taken in the evening

### Treatment Strategies for Refractory Depression

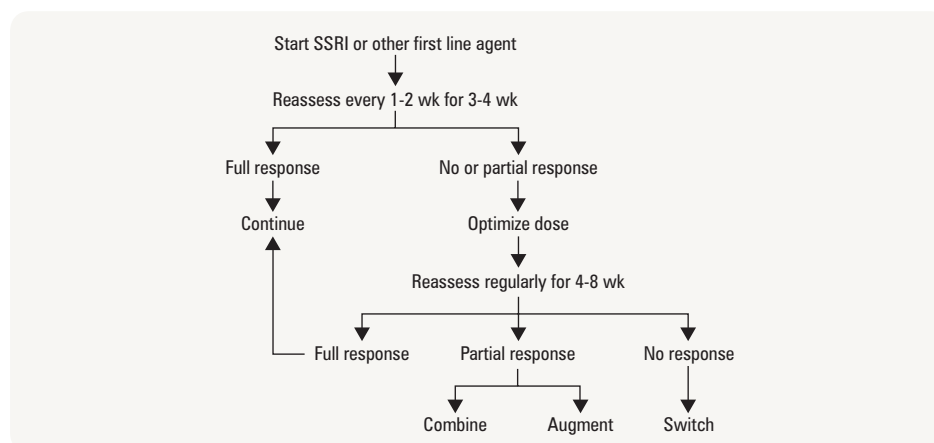


Figure 3. Treatment of depression

- **optimization:** ensuring adequate drug doses for the individual
- **augmentation:** the addition of a medication that is not considered an antidepressant to an antidepressant regimen (e.g. thyroid hormone, lithium, atypical antipsychotics)
- **combination:** the addition of another antidepressant to an existing treatment regimen (e.g. the addition of bupropion to an SSRI or SNRI)
- **substitute:** change in the primary antidepressant (within or outside a class)
- **note:** it is important to fully treat the symptoms of depression in order to decrease rates and severity of relapses



#### How Long to Treat?

- **6-12 mo:** if first or second episode.
- **2 yr:** if third episode, elderly, psychotic features, refractory depression, > 2 episodes in 5 yr.



#### Psychopharmacology of SSRIs

Post-Synaptic Serotonin Receptor Stimulated	Effect/Side Effect
5HT1A centrally	<ul style="list-style-type: none"> <li>• Relief of depression</li> <li>• Anxiolytic effect</li> </ul>
5HT2A in spinal cord	<ul style="list-style-type: none"> <li>• Sexual dysfunction: delayed ejaculation, anorgasmia, decreased interest/libido</li> </ul>
5HT2C/5HT2A in brain	<ul style="list-style-type: none"> <li>• Activation: anxiety, insomnia</li> <li>• Worst with fluoxetine, paroxetine</li> <li>• Warn patients anxiety may worsen in first 1-2 wk of treatment</li> </ul>
5HT3A in gut	<ul style="list-style-type: none"> <li>• GI upset: nausea, vomiting, bloating</li> <li>• Take with food</li> </ul>



Table 22. Commonly Used Antidepressants

	TCA	SSRI	MAOI	SNRI
<b>Considerations</b>	OCD (clomipramine), melancholic depression	Anxiety states, OCD, eating disorders, seasonal depression, typical and atypical depression	For moderate/severe depression that does not respond to SSRI, atypical depression	Depression, anxiety disorders
<b>Mode of Action</b>	Block norepinephrine and serotonin reuptake	Block serotonin reuptake only	Irreversible inhibition of monoamine oxidase A and B Leads to ↑ norepinephrine and serotonin	Block norepinephrine and serotonin reuptake
<b>Side Effects</b>	Anticholinergic effects: (see Table 19) Noradrenergic effects: tremors, tachycardia, sweating, insomnia, erectile and ejaculation problems $\alpha$ -1 adrenergic effects: orthostatic hypotension Antihistamine effects: sedation, weight gain CNS: sedation, stimulation, ↓ seizure threshold CVS: ↑ HR, conduction delay	Fewer than TCA, therefore increased compliance CNS: restlessness, tremor, insomnia, headache, drowsiness GI: N/V, diarrhea, abdominal cramps, weight loss Sexual dysfunction: impotence, anorgasmia CVS: increased HR, conduction delay, serotonin syndrome, EPS, SIADH	Hypertensive crises with tyramine rich foods (e.g. wine, cheese), headache, flushes, palpitations, N/V, photophobia Dizziness, reflex tachycardia, postural hypotension, sedation, insomnia Weight gain Social dysfunction Energizing Minimal anticholinergic and antihistamine effects	Low dose side effects include insomnia (serotonergic) Higher dose side effects include: tremors, tachycardia, sweating, insomnia, dose-dependent increase in diastolic BP (noradrenergic)
<b>Risk in Overdose</b>	Toxic in OD 3 times therapeutic dose is lethal Presentation: anticholinergic effects, CNS stimulation, then depression and seizures ECG: prolonged QT (duration reflects severity) Treatment: activated charcoal, cathartics, supportive treatment, IV diazepam for seizure, physostigmine salicylate for coma Do not give ipecac, as can cause rapid neurologic deterioration and seizures	Relatively safe in OD	Toxic in OD, but wider margin of safety than TCA	Tachycardia and N/V seen in acute overdose
<b>Drug Interactions</b>	MAOI, SSRI EtOH	SSRIs inhibit P450 enzymes, therefore will affect levels of drugs metabolized by P450 system	EtOH Hypertensive crises with noradrenergic medications (e.g. TCA, decongestants, amphetamines) Serotonin syndrome with serotonergic drugs (e.g. SSRI, tryptophan, dextromethorphan)	MAOI, SSRI Does not seem to inhibit P450 system
	NDRI	RIMA	NASSA	
<b>Considerations</b>	Depression, seasonal depression	Depression unresponsive to other therapies	Useful in patients with insomnia, agitation or depression with cachexia	
<b>Mode of Action</b>	Block norepinephrine and dopamine reuptake	Reversible inhibitor of monoamine oxidase A Leads to ↑ norepinephrine and serotonin	Enhance central noradrenergic and serotonergic activity by inhibiting presynaptic $\alpha$ -2 adrenergic receptors	
<b>Side Effects</b>	CNS: dizziness, headache, tremor, insomnia CVS: dysrhythmia, hypertension GI: dry mouth, N/V, constipation, ↓ appetite Other: agitation, anxiety, anaphylactoid reaction	CNS: dizziness, headache, tremor, insomnia CVS: dysrhythmia, hypotension GI: dry mouth, N/V, diarrhea, abdominal pain, dyspepsia GU: delayed ejaculation Other: diaphoresis	CNS: somnolence, dizziness, seizure (rare) Endocrine: ↑ cholesterol, ↑ triglycerides GI: constipation, ↑ ALT	
<b>Risk in Overdose</b>	Tremors and seizures seen in acute overdose	Risk of fatal overdose when combined with citalopram or clomipramine	Mild symptoms with overdose	
<b>Drug Interactions</b>	MAOI Drugs that reduce seizure threshold: antipsychotics, systemic steroids, quinolone antibiotics, antimalarial drugs	MAOI, SSRI, TCA Opioids	MAOI, SSRI, SNRI, RIMA	

## Serotonin Syndrome

- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as SSRI+MAOI, SSRI+tryptophan, MAOI+meperidine, MAOI+tryptophan
- rare but potentially life-threatening adverse reaction to SSRIs, especially when switching from an SSRI to an MAOI
- symptoms include nausea, diarrhea, palpitations, chills, restlessness, confusion, and lethargy but can progress to myoclonus, hyperthermia, rigor and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS (see sidebar, PS44)

## Discontinuation Syndrome

- caused by the abrupt cessation of an antidepressant
- observed most frequently with paroxetine, fluvoxamine, and venlafaxine
- symptoms usually begin within 1-3 d and include: anxiety, insomnia, irritability, mood lability, N/V, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy and myalgia
- treatment: symptoms may last between 1-3 wk, but can be relieved within 24 h by restarting antidepressant therapy at the same dose the patient was taking and initiating a slow taper over several weeks
- consider drug with longer half-life such as fluoxetine



### Symptoms of Antidepressant Discontinuation

#### FINISH

Flu-like symptoms  
Insomnia  
Nausea  
Imbalance  
Sensory disturbances  
Hyperarousal (anxiety/agitation)



### Sequenced Treatment Alternatives to Relieve Depression

*Journal of Psychosocial Nursing* 2008; 46:21-24

**Study:** Prospective randomized anti-depressant treatment trial.

**Patients:** 4000 patients with major depressive disorder.

**Objective:** To compare the efficacy and tolerability of various antidepressant therapies through four sequential treatment levels.

**Intervention:** Level 1-citalopram → if relapse → Level 2-citalopram + bupropion SR, sertraline, venlafaxine XR, or cognitive psychotherapy. Level 2A-switch to bupropion or venlafaxine XR. Level 3-either mirtazapine or nortriptyline + lithium, T3. Level 4-tranylcypromine or venlafaxine XR + mirtazapine.

**Results:** Remission rates were 28% for Level 1, 17% for Level 2, 12-25% for Level 3, and 7-14% for Level 4. When more treatment steps are required, there are lower remission rates, greater degrees of tolerance, and higher rates of relapse.



Long term lithium use can lead to a nephropathy and diabetes insipidus in some patients.



### Lithium Side Effects

#### LITHIUM

Leukocytosis  
Insipidus (diabetes)  
Tremor, teratogenicity  
Hypothyroidism  
Increased weight  
"V"omiting, nausea  
Miscellaneous (e.g. ECG changes, acne)

## Mood Stabilizers

### First-Line

#### Lithium or Valproic Acid (± antipsychotic)

- before initiating, get baseline: CBC, ECG (if patient >45 yr old or cardiovascular risk), urinalysis, BUN, Cr, electrolytes, TSH
- before initiating lithium: screen for pregnancy, thyroid disease, seizure disorder, neurological, renal, cardiovascular diseases
- may need acute coverage with benzodiazepines or antipsychotics
- use carbamazepine in non-responders and rapid cycling bipolar disorder
- can combine lithium and carbamazepine or valproic acid safely in lithium non-responders
- olanzapine may be used as a mood stabilizer, in conjunction with other mood stabilizers
- lithium and lamotrigine have established antidepressant efficacy

#### Lithium Toxicity (see Table 23)

- clinical diagnosis as toxicity can occur at therapeutic levels
- **common causes**
  - overdose
  - sodium or fluid loss
  - concurrent medical illness
- **clinical presentation**
  - GI: severe nausea/vomiting and diarrhea
  - cerebellar: ataxia, slurred speech, lack of coordination
  - cerebral: drowsiness, myoclonus, choreiform or Parkinsonian movements, upper motor neuron signs, seizures, delirium, coma
- **management**
  - discontinue lithium for several doses and begin again at a lower dose when lithium level has fallen to a non-toxic range
  - serum lithium levels, BUN, electrolytes
  - saline infusion
  - hemodialysis if lithium >2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 h, or deterioration

### Second-Line/Adjuvant Mood Stabilizers

Lithium, lamotrigine, divalproex, carbamazepine

**Table 23. Commonly Used Mood Stabilizers**

	<b>Lithium</b>	<b>Lamotrigine (Lamictal®)</b>	<b>Divalproex (Epival®)</b>	<b>Carbamazepine (Tegretol®)</b>
<b>Indications</b>	Maintenance therapy of bipolar disorder Treatment of acute mania Augmentation of antidepressants in MDE and OCD Schizoaffective disorder Chronic aggression and antisocial behaviour Recurrent depression	Treatment of bipolar disorder	Maintenance therapy of bipolar disorder Treatment of acute mania Rapid cycling bipolar disorder Mixed phase/Dysphoric mania	Maintenance therapy of bipolar disorder Treatment of acute mania Rapid cycling bipolar disorder
<b>Mode of Action</b>	Unknown Therapeutic response within 7-14 d	May inhibit 5-HT <sub>3</sub> receptors May potentiate DA activity	Depresses synaptic transmission Raises seizure threshold	Depresses synaptic transmission Raises seizure threshold
<b>Dosage</b>	Adult: 600-1500 mg/d Geriatric: 150-600 mg/d Usually daily dosing	Starting: 12.5-15 mg/d Daily dose: 100-200 mg/d Dose adjusted in patients taking other anticonvulsants	750-2500 mg/d Usually tid dosing	400-1600 mg/d Usually bid or tid dosing
<b>Therapeutic Level</b>	Adult: 0.5-1.2 mmol/L (1.0-1.25 mmol/L for acute mania) Geriatric: 0.3-0.8 mmol/L	Therapeutic plasma level not established Dosing based on therapeutic response	17-50 mmol/L	350-700 µmol/L
<b>Monitoring</b>	Monitor serum levels until therapeutic (always wait 12 h after dose) Then monitor biweekly or monthly until a steady state is reached, then q2mo Monitor thyroid function q6mo, creatinine q6mo, urinalysis q1yr	Monitor for suicidality, particularly when initiating treatment	LFTs weekly x 1 mo, then monthly, due to risk of liver dysfunction Watch for signs of liver dysfunction: nausea, edema, malaise	Weekly blood counts for first month, due to risk of agranulocytosis Watch for signs of blood dyscrasias: fever, rash, sore throat, easy bruising
<b>Side Effects</b>	GI: N/V, diarrhea, stomach pain GU: polyuria, polydipsia, GN, renal failure, nephrogenic DI CNS: fine tremor, lethargy, fatigue, headache Hematologic: reversible leukocytosis Other: teratogenic (Ebstein's anomaly), weight gain, edema, psoriasis, hypothyroidism, hair thinning, muscle weakness, ECG changes	GI: N/V, diarrhea CNS: ataxia, dizziness, diplopia, headache, somnolence Skin: rash (should d/c drug because of risk of Stevens-Johnson syndrome), increased lamotrigine levels = increased risk of rash Other: anxiety	GI: liver dysfunction, N/V, diarrhea CNS: ataxia, drowsiness, tremor, sedation, cognitive blurring Other: hair loss, weight gain, transient thrombocytopenia, neural tube defects when used in pregnancy	GI: N/V, diarrhea, hepatic toxicity CNS: ataxia, dizziness, slurred speech, drowsiness, confusion, nystagmus, diplopia Hematologic: transient leukopenia (10%), agranulocytosis, aplastic anemia Skin: rash (5% risk; should d/c drug because of risk of Stevens-Johnson syndrome) Other: neural tube defects when used in pregnancy
<b>Interactions</b>	NSAIDs decrease clearance		OCP	OCP

## Anxiolytics

- anxiolytics mask or alleviate symptoms; they do not cure them
- **indications**
  - short term treatment of transient forms of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, organic brain syndrome (agitation in dementia), EPS and akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders
- **relative contraindications**
  - major depression (except as an adjunct to other treatment), history of drug/alcohol abuse, pregnancy, breast feeding
- **mechanism of action**
  - benzodiazepines: potentiate binding of GABA to its receptors; results in decreased neuronal activity
  - buspirone: partial agonist of 5-HT<sub>1A</sub> receptors

### Benzodiazepines

- should be used for limited periods (weeks-months) to avoid dependence
- all benzodiazepines are sedating; be wary in use for the elderly
- have similar efficacy, so choice depends on half-life, metabolites and route of administration, OD or bid
- taper slowly over weeks-mo because they can cause withdrawal reactions
  - low dose withdrawal: tachycardia, hypertension, panic, insomnia, anxiety, impaired memory and concentration, perceptual disturbances
  - high dose withdrawal: hyperpyrexia, seizures, psychosis, death
- avoid alcohol because of potentiation of CNS depression; caution with drinking and use of machinery

- **side effects**
  - CNS: drowsiness, cognitive impairment, reduced motor coordination, memory impairment
  - physical dependence, tolerance develops
- **withdrawal**
  - symptoms: anxiety, insomnia, autonomic hyperactivity (less common)
  - onset: 1-2 d (short-acting), 2-4 d (long-acting)
  - duration: weeks/months
  - complications: above 50 mg diazepam/day: seizures, delirium, arrhythmias, psychosis
  - management: taper with long-acting benzodiazepine
  - similar to but less severe than alcohol withdrawal; can be fatal
- **overdose**
  - commonly used drug in overdose
    - ♦ overdose is rarely fatal
    - ♦ benzodiazepines are more dangerous and may cause death when combined with alcohol, other CNS depressants or TCAs

### Benzodiazepine Antagonist – Flumazenil (Anexate®)

- use for suspected benzodiazepine overdose
- specific antagonist at the benzodiazepine receptor site

### Buspirone (Buspar®)

- **primary use:** GAD
- may be preferred over benzodiazepines because:
  - non-sedating
  - no interaction with alcohol
  - does not alter seizure threshold
  - not prone to abuse
- **onset of action:** 2 wk
- **side effects:** dizziness, drowsiness, nausea, headache, nervousness, EPS

**Table 24. Common Anxiolytics**

Class	Drug	Dose Range (mg/d)	t <sub>1/2</sub> (h)	Appropriate Use
<b>Benzodiazepines</b>				
Long-acting	clonazepam (Rivotril®)	0.25-4	18-50	Akathisia, generalized anxiety, seizure prevention, panic disorder
	diazepam (Valium®)	2-40	30-100	Generalized anxiety, seizure prevention, muscle relaxant, alcohol withdrawal
	chlordiazepoxide (Librium®)	5-300	30-100	Sleep, anxiety, alcohol withdrawal
	flurazepam (Dalmane®)	15-30	50-160	Sleep
Short-acting	alprazolam (Xanax®)	0.25-4.0	6-20	Panic disorder, high dependency rate
	lorazepam (Ativan®)	0.5-6.0	10-20	Sleep, generalized anxiety, akathisia, alcohol withdrawal, sublingual available for very rapid action
	oxazepam (Serax®)	10-120	8-12	Sleep, generalized anxiety, alcohol withdrawal
	temazepam (Restoril®)	7.5-30	8-20	Sleep
	triazolam (Halcion®)	0.125-0.5	1.5-5	Shortest t <sub>1/2</sub> , rapid sleep, but rebound insomnia
<b>Azapirones</b>				
	buspirone (Buspar®)	20-60	2-11	Generalized anxiety
	zopiclone (Imovane®)	5-7.5	3.8-6.5	Sleep



#### Geriatric Benzodiazepines

##### LOT

Lorazepam  
Oxazepam  
Temazepam

Safe in liver disease because not metabolized by liver



#### Benzodiazepines used for Alcohol Withdrawal

- Diazepam 20 mg PO/IV q1h prn
- Lorazepam 2-5 mg PO/IV/SL for patients with liver disease, chronic lung disease, or elderly



#### ECT in Society

Prior to the 1940's, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by barbaric depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients struggling with mental illness.

## Electroconvulsive Therapy

- induction of a grand mal seizure using an electrical pulse through the brain while the patient is under general anesthesia with a muscle relaxant
- unilateral vs. bilateral electrode placement
- **indications**
  - depression refractory to adequate pharmacological trial
  - high suicide risk
  - medical risk in addition to depression (dehydration, electrolytes, pregnancy)
  - previous good response to ECT
  - familial response to ECT
  - elderly

- psychotic depression
- catatonic features
- marked vegetative features
- acute schizophrenia
- mania unresponsive to medications
- **side effects:** risk of anesthesia, memory loss (may be retrograde and/or anterograde, tends to resolve by 6 to 9 mo, permanent impairment controversial), headaches, myalgias
- evidence that unilateral ECT causes less memory loss than bilateral but may not be as effective
- **contraindications:** increased intracranial pressure



#### Efficacy of ECT in Depression: A Meta-Analytic Review

*J of ECT* 2004; 20:13-20

**Study:** Meta-analysis of randomized and non-randomized control trials.

**Patients:** Individuals with unipolar and bipolar depression.

**Methods:** MEDLINE search for relevant papers from 1966-2003.

**Main Outcomes:** The Hamilton Depression Rating scale was used to determine response to treatment.

**Results:** ECT was found to be superior to simulated ECT, placebo, TCAs, MAOIs, and anti-depressants in general.

**Summary:** ECT is an efficacious treatment modality, particularly in severe and treatment-resistant depression.

## Experimental Therapies

### Deep Brain Stimulation (DBS)

- constant electrical stimulation of neuroanatomical targets that have been identified in the biological model of depression
- areas identified include the nucleus accumbens, internal capsule and subgenual cingulate cortex
- parameters such as active electrode location, pulse width, frequency and voltage may be manipulated

### Transcranial Magnetic Stimulation (TMS)

- non-invasive magnetic stimulation of superficial neurons in the frontal cortex (main target: dorsolateral prefrontal cortex) hypothesized to normalize cortical activity in depressed patients
- meta-analyses show modest acute efficacy

### Vagal Nerve Stimulation

- an invasive surgical procedure: a battery powered pulse generator is implanted in the chest wall and connected to an electrode that is attached around one (typically the left) vagus nerve
- meta-analyses show a greater response and remission rates for treatment resistant depression if combined with usual treatment (versus usual treatment alone)
- not indicated for use in acute illness

## Canadian Legal Issues



## Common Forms

Table 25. Common Forms Under the *Mental Health Act* (in Ontario)

Form	Who Signs	When	Expiration Date	Right of Patient to Review Board Hearing	Options Before Form Expires
<b>Form 1:</b> Application by physician to hospitalize a patient for psychiatric assessment against his/her will to a schedule 1 facility (Form 42 given to patient)	Any MD	Within 7 d after examination of the patient	72 h after hospitalization Void if not implemented within 7 d	No	Form 3 or voluntary admission (Form 5) or Send home ± Follow up
<b>Form 2:</b> Order for hospitalization and medical examination against his/her will by Justice of the Peace	Justice of the Peace	No statutory time restriction	7 d from when completed Purpose of form is complete once patient brought to hospital	No	Form 1 or Send home ± Follow up
<b>Form 3:</b> Certificate of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)	Attending MD (different than MD who completed Form 1)	Before expiration of Form 1 Any time to change status of an involuntary patient	14 d	Yes (within 48 h)	Form 4 or Form 5



#### Form 1: Application for Psychiatric Assessment

- Filled out when a patient is suspected of being an imminent harm to themselves (suicide) or others (homicide) or when they are incapable of self-care (e.g. not dressed for freezing weather) and are suffering from an apparent mental disorder
- Based on any combination of the physician's own observations and facts communicated by others
- Box A or Box B completed
- **Box A:** Serious Harm Test
- The Past/Present Test assesses current behaviours/threats/attempts
- The Future Test assesses the likelihood of serious harm occurring as a result of the presenting mental disorder. In this section, one should document evidence of the mental disorder
- **Box B:** Patients with a known mental disorder, who are incapable of consenting to treatment (existing substitute decision-maker), have previously received treatment and improved, and are currently at risk of serious harm due to the same mental disorder

**Table 25. Common Forms Under the Mental Health Act (in Ontario)** (continued)

Form	Who Signs	When	Expiration Date	Right of Patient to Review Board Hearing	Options Before Form Expires
<b>Form 4:</b> Certificate of renewal of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)	Attending MD following patient on Form 3	Prior to expiration of Form 3	First: 1 mo Second: 2 mo Third: 3 mo (max)	Yes (within 48 h)	Form 4 or Form 5
<b>Form 5:</b> Change to informal/voluntary status	Attending MD following patient on Form 3/4	Whenever deemed appropriate	N/A	N/A	N/A
<b>Form 30:</b> Notice to patient on certification on Form 3 or Form 4	Attending MD	At time of completion of Form 3 or 4	N/A	Yes	N/A
<b>Form 33:</b> Notice to patient that patient is incompetent to consent to treatment of mental disorder and/or management of property	Attending MD	Whenever deemed appropriate	N/A	N/A	N/A

\* Schedule 1 Facilities: Able to provide intensive inpatient and outpatient care

## Consent

- see [Ethical, Legal and Organizational Aspects of Medicine](#), ELOAM5



## Community Treatment Order (CTO)

- known as “Brian’s Law,” Ontario passed legislature regarding CTOs on December 1, 2000
- similar CTOs have been implemented in Saskatchewan (1995), Manitoba (1997) and British Columbia (1999)
- purpose: to provide a person who suffers from a serious mental disorder with a comprehensive plan of community-based treatment and supervision that is less restrictive than being detained in a psychiatric facility
- intended for those who:
  - as a result of their serious mental disorder, experience a pattern of admission to a psychiatric facility where their condition is usually stabilized
  - after being released, these patients often lack supervision and stop treatment
  - due to the destabilization of their condition, these patients usually require re-admission to hospital
- criteria for a physician to issue a CTO
  - patient with a prior history of hospitalization
  - a community treatment plan for the person has been made
  - examination by a physician within the previous 72 h before entering into the CTO plan
  - ability of the person subject to the CTO to comply with it
  - consultation with a rights adviser and consent of the person and the person’s substitute decision maker, if any
- CTOs are valid for 6 mo unless they are renewed or terminated at an earlier date
  - where the person fails to comply with the CTO
  - when the person or his/her substitute decision-maker withdraws consent to the community treatment plan
- CTO process is consent-based and all statutory protections governing informed consent apply
- the rights of a person subject to a CTO include:
  - the right to a review by the Consent and Capacity Board with appeal to the courts each time a CTO is issued or renewed
  - a mandatory review by the Consent and Capacity Board every second time a CTO is renewed
  - the right to request a re-examination by the issuing physician to determine if the CTO is still necessary for the person to live in the community
  - the right to review findings of incapacity to consent to treatment
  - provisions for rights advice



## Duty to Inform/Warn

- see [Ethical, Legal, and Organizational Aspects of Medicine](#), ELOAM9



## References

### Textbooks

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. (text revision). Washington: American Psychiatric Publishing, 2000.
- Conley RR, Kelly DL. Pharmacologic treatment of schizophrenia, 1st ed. USA: Professional Communications, 2000.
- Kahan M, Wilson L. Managing alcohol, tobacco and other drug problems: a pocket guide for physicians and nurses. Toronto: Centre for Addiction and Mental Health, 2002.
- Koch T. A tour of the psychotropics, 4th ed. Toronto: Mental Health Service, St Michael's Hospital.
- Piisakka SR, Greenhill LL, Crismon ML, et al. Textbook of psychiatry. London: Oxford University Press; c1997. p109.
- Stahl SM. Psychopharmacology of antipsychotics. London: Martin Dunitz, c1999.
- Tasman. Psychiatry, 1st ed. Wiley, c1997. p208.
- Zimmerman, M. Interview guide for evaluating DSM-IV psychiatric disorders and the mental status examination. East Greenwich: Psych Products Press, 1994.

### Journals

- Abel KM, Drake R, Goldstein, JM. Sex differences in schizophrenia. *Int Rev Psychiatry* 2010;22:417-428.
- Ball JR, Mitchell PB, Cory JC, Skilecorn A, Smith M, Malhi GS. A randomized controlled trial of cognitive therapy for bipolar disorder: focus on long-term change. *J Clin Psychiat* 2006;67:277-286.
- Clarke MC, Harley M, Cannon M. The role of obstetric events in schizophrenia. *Schizophr Bull* 2006;32:3-8.
- Clinical Practice Guidelines: treatment of schizophrenia. *Can J Psychiat* 2005;50(Suppl1):19-28.
- Croxtall JD. Aripiprazole: a review of its use in the management of schizophrenia in adults. *CNS Drugs* 2012;26:155-183.
- DeRubeis RJ, et al. Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Arch Gen Psychiat* 2005;62:409-416.
- Ditto KE. SSRI discontinuation syndrome: awareness as an approach to prevention. *Postgrad Med* 2003;114:79-84.
- Folstein MF, Folstein SE and McHugh PR. Mini-mental state: a practical method for grading the state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
- Gliatto MF and Rai AK. Evaluation and treatment of patients with suicidal intention. *Am Fam Physician* 1999;59:1500-1514.
- Hembree EA, Foa EB. Post traumatic stress disorder: psychological factors and psychosocial interventions. *J Clin Psychiat* 2000;61(Suppl7):33-39.
- Graham-Knight D, Karch AM. Pharm party. *Am J Nursing* 2007;107:79.
- Herrmann N. Recommendations for the Management of Behavioural and Psychological Symptoms of Dementia. *Can J Neurol Sci* 2001;28(Suppl1):96-107.
- Howland RH. Sequenced treatment alternatives to relieve depression (STAR\*D). Part 2: study outcomes. *J Psychosoc Nurs Ment Health Serv* 2008;46:21-24.
- Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. *Am J Psychiat* 1999;156:286-293.
- Krupnick JL, et al. The role of the therapeutic alliance in psychotherapy and pharmacotherapy outcome: findings in the National Institute of Mental Health treatment of depression collaborative research program. *J Consult Clin Psychol* 1996;64:532-539.
- Kuepper R, van Os J, Lieb R, Wittchen HU, Høfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ* 2011;342:d738.
- Lieberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *NEJM* 2005;353:1209-1223.
- Linde K, Berner MM, Kriston L. St John's wort for major depression. *Cochrane DB Syst Rev* 2008;4:CD000448.
- Lineham MM, et al. Two-year randomized controlled trial and follow-up of dialectical behaviour therapy vs. therapy by experts for suicidal behaviours and borderline personality disorder. *Arch Gen Psychiat*. 2006;63:757-766.
- Lopez M and Torpac MG. The Texas children's medication algorithm project: report of the Texas consensus conference panel on medication treatment of childhood attention-deficit/hyperactivity disorder. Part I. *Am Acad Child Adolescent Psychiat* 2000;39:908-919.
- March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004;292:807-820.
- Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007;370:319-328.
- MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiat* 1999;56:1073-1086.
- National Institute on Drug Abuse. Research report series: methamphetamine abuse and addiction. reprinted 2002 Jan. NIH Publication No.: 02-4210.
- Noble J. Textbook of primary care medicine, 3rd ed. Mosby, c2000. p466,470.
- Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. *J ECT* 2004;20:13-20.
- Patterson CJ, Gauthier S, Bergman H, et al. Canadian Consensus Conference on Dementia: A Physician's Guide to Using the Recommendations. *CMAJ* 1999;160:1738-1742.
- Patten SB, Wang JL, Williams JV, Currie S, Beck CA, Maxwell CJ, El-Guebaly N. Descriptive epidemiology of major depression in Canada. 2006;51:84-90.
- Perkins DO, Gu H, Boteva K, et al. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiat*. 2005;162:1785-1804.
- Reinares M, Rosa AR, Franco C, Goikolea JM, Fountoulakis K, Siamouli M, et al. A systematic review on the role of anticonvulsants in the treatment of acute bipolar depression. *Intl J Neuropsychopharm* 2012;10:1-12.
- Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934-1943.
- Stoner SC and Pace HA. Asenapine: a clinical review of a second-generation antipsychotic. *Clinical Therapeutics* 2012;34:1023-1040.
- Szewczyk M. Women's health: depression and related disorders. *Primary Care* 1997;24:83-101.
- Troiden R. The formation of homosexual identities. *J Homosexuality* 1989;17:43-73.
- Warneke L. Breaking the urges of obsessive-compulsive disorder. *Can J Diag* 1996;13:107-120.
- Weller EB, Weller RA, Fristad MA. Bipolar disorder in children: misdiagnosis, underdiagnosis, and future directions. *J Am Acad Child Adolescent Psychiat* 1995;34:709-714.
- Whittington CJ, Kendall T, Fonagy P, et al. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363:1341-1345.

### Websites

- Long. PW. Internet mental health (Internet). Place unknown: Publisher unknown (c1995-2011; cited 2003). Available from: <http://www.mentalhealth.com/>.

Amanda Goldberg, Sicong Huang and Joanna Willms, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Meyer Balter, staff editor

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Respiratory Failure</b> . . . . .	<b>24</b>
<b>Approach to the Respiratory Patient</b> . . . . .	<b>2</b>	Hypoxemic Respiratory Failure	
Basic Anatomy Review		Hypercapnic Respiratory Failure	
Differential Diagnoses of Common Presentations		Acute Respiratory Distress Syndrome (ARDS)	
Pulmonary Function Tests (PFTs)		Mechanical Ventilation	
Chest X-Rays			
Arterial Blood Gases		<b>Neoplasms</b> . . . . .	<b>27</b>
<b>Diseases of Airway Obstruction</b> . . . . .	<b>6</b>	Lung Cancer	
Pneumonia		Approach to the Solitary Pulmonary Nodule	
Asthma		<b>Sleep-Related Breathing Disorders</b> . . . . .	<b>31</b>
Chronic Obstructive Pulmonary Disease (COPD)		Hypoventilation Syndromes	
Bronchiectasis		Sleep Apnea	
Cystic Fibrosis (CF)		<b>Introduction to Intensive Care</b> . . . . .	<b>32</b>
<b>Interstitial Lung Disease (ILD)</b> . . . . .	<b>12</b>	ICU Basics	
Unknown Etiologic Agents		Organ Failure	
Idiopathic Pulmonary Fibrosis (IPF)		Shock	
Sarcoidosis		Sepsis	
Known Etiologic Agents		<b>Common Medications</b> . . . . .	<b>34</b>
Hypersensitivity Pneumonitis		<b>Landmark Respirology Trials</b> . . . . .	<b>35</b>
Pneumoconioses		<b>References</b> . . . . .	<b>36</b>
ILD Associated with Drugs or Treatments			
<b>Pulmonary Vascular Disease</b> . . . . .	<b>16</b>		
Pulmonary Hypertension			
Idiopathic Pulmonary Arterial Hypertension			
Pulmonary Embolism (PE)			
Pulmonary Vasculitis			
Pulmonary Edema			
<b>Diseases of the Mediastinum and Pleura</b> . . .	<b>20</b>		
Mediastinal Masses			
Mediastinitis			
Pleural Effusions			
Complicated Parapneumonic Effusion			
Empyema			
Atelectasis			
Pneumothorax			
Asbestos-Related Pleural Disease and			
Mesothelioma			

## Acronyms

A-a	alveolar arterial	DIC	disseminated intravascular coagulation	MEP	maximum expiratory pressure	PVC	premature ventricular contraction
A-aDO <sub>2</sub>	alveolar-arterial oxygen diffusion gradient	DL <sub>CO</sub>	carbon monoxide diffusing capacity of lung	MIP	maximum inspiratory pressure	RA	rheumatoid arthritis
ABG	arterial blood gas	EBUS	endobronchial ultrasound	MSA	mixed sleep apnea	RAD	right axis deviation
ACEI	angiotensin converting enzyme inhibitor	ECMO	extracorporeal membrane oxygenation	MSK	musculoskeletal	RAP	right atrial pressure
ACV	assist-control ventilation	ERV	expiratory reserve volume	N/V	nausea and vomiting	RBBB	right bundle branch block
AECOPD	acute exacerbation of COPD	ETT	endotracheal tube	NPPV	non-invasive positive pressure ventilation	RF	rheumatoid factor
AFB	acid-fast bacillus	FEF	forced expiratory flow rate	NSCLC	non-small cell lung cancer	RV	residual volume
AFP	alpha-fetoprotein	FEV <sub>1</sub>	forced expiratory volume in 1 second	NTT	nasotracheal tube	RVEDV	right ventricular end diastolic volume
AHI	apnea hypopnea index	FIO <sub>2</sub>	fraction of oxygen in inspired air	OC	oral contraceptive pill	RVH	right ventricular hypertrophy
ALS	amyotrophic lateral sclerosis	FRG	functional residual capacity	OSA	obstructive sleep apnea	RVSP	right ventricular systolic pressure
ANA	antinuclear antibody	GBM	glomerular basement membrane	PPV	non-invasive positive pressure ventilation	SCC	squamous cell carcinoma
ANCA	anti-neutrophil cytoplasmic antibody	GERD	gastroesophageal reflux disease	NSCLC	non-small cell lung cancer	SCLC	small cell lung cancer
APTT	activated partial thromboplastin time	H/A	headache	NTT	nasotracheal tube	S <sub>2</sub> O <sub>2</sub>	central venous oxygen saturation
ARDS	acute respiratory distress syndrome	HPA	human platelet antigen	OC	oral contraceptive pill	SIMV	synchronous intermittent mandatory ventilation
ASA	acetylsalicylic acid (Aspirin®)	HRT	hormone replacement therapy	OSA	obstructive sleep apnea	SIRS	systemic inflammatory response syndrome
ASD	atrial septal defect	IBD	inflammatory bowel disease	PA	posteroanterior	SV	stroke volume
AV	arteriovenous	IC	inspiratory capacity	P <sub>a</sub> CO <sub>2</sub>	arterial partial pressure of carbon dioxide	SVC	superior vena cava
AVM	arteriovenous malformation	ICP	intracranial pressure	P <sub>a</sub> O <sub>2</sub>	arterial partial pressure of oxygen	SVRI	systemic vascular resistance index
AVN	avascular necrosis	ICS	inhaled corticosteroid	P <sub>atm</sub>	atmospheric pressure	TB	tuberculosis
BG	blood glucose	ILD	interstitial lung disease	PCP	pneumocystis carinii pneumonia	TCA	tricyclic antidepressant
BIPAP	bilevel positive airway pressure	IPF	idiopathic pulmonary fibrosis	PCWP	pressure control ventilation	TLC	total lung capacity
BOOP	bronchiolitis obliterans with organizing pneumonia	LAAC	long-acting anti-cholinergic	PDA	patent ductus arteriosus	TNM	tumour, node, metastasis
BSA	body surface area	LABA	long-acting beta-agonist	PEEP	positive end expiratory pressure	TPN	total parenteral nutrition
CA	cancer	LLN	lower limit of normal	PEF	peak expiratory flow	UC	ulcerative colitis
CCB	calcium channel blocker	LMWH	low molecular weight heparin	PFT	pulmonary function tests	URTI	upper respiratory tract infection
CD	Crohn's disease	LTRA	leukotriene receptor antagonist	PMNs	polymorphonuclear cells	VATS	video-assisted thorascopic surgery
CHF	congestive heart failure	LV	left ventricle	PP	pulse pressure	V/Q	ventilation-to-perfusion
CI	cardiac index	LVEDP	left ventricular end diastolic pressure	PSV	pressure support ventilation	VC	vital capacity
CO	cardiac output	LVF	left ventricular failure	PTH	parathyroid hormone	VSD	ventricular septal defect
COP	cryptogenic organizing pneumonia	MAC	Mycobacterium avium complex	PTT	partial thromboplastin time	VTE	venous thromboembolism
CPAP	continuous positive airway pressure	MDI	metered dose inhaler	PUD	peptic ulcer disease	V <sub>T</sub>	tidal volume
CSA	central sleep apnea						
CVD	cardiovascular disease						
CVP	central venous pressure						
CWP	coal worker's pneumoconiosis						

## Approach to the Respiratory Patient

### Basic Anatomy Review

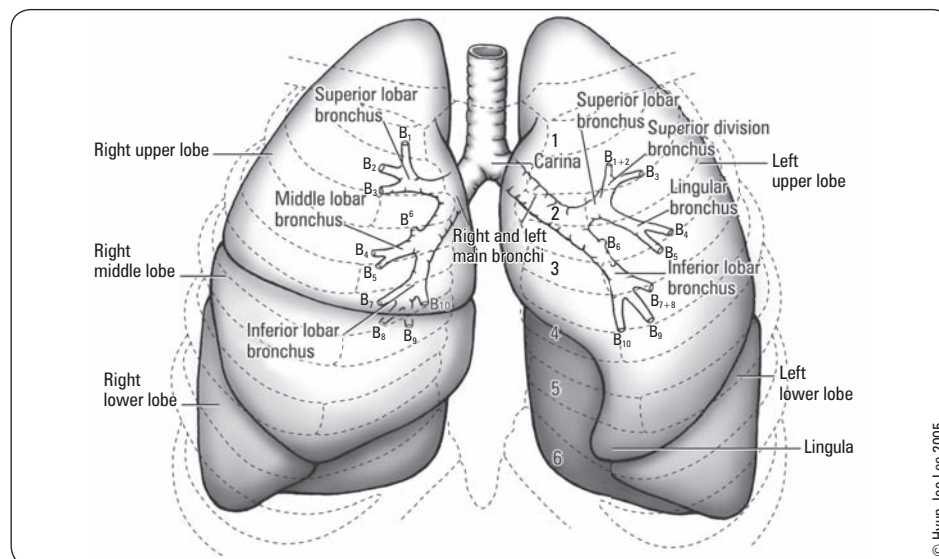


Figure 1. Lung lobes and bronchi

#### Respiration Pattern

**Normal**

**Obstructive** (prolonged expiration)

- Asthma, COPD

**Bradypnea** (slow respiratory rate)

- Drug-induced respiratory depression
- Diabetic coma (nonketotic)
- Increased ICP

**Kussmaul's Breathing** (fast and deep)

- Metabolic acidosis
- Exercise
- Anxiety

**Biot's/Ataxic** (irregular with long apneic periods)

- Drug-induced respiratory depression
- Increased ICP
- Brain damage, especially medullary

**Cheyne-Stokes Breathing** (changing rates and depths with apneic periods)

- Drug-induced respiratory depression
- Brain damage (especially cerebral)
- CHF
- Uremia

**Apneustic** (prolonged inspiratory pause)

- Pontine lesion

© Bonnie Tang 2012

Figure 2. Respiration patterns in normal and disease states

## Differential Diagnoses of Common Presentations

Table 1. Differential Diagnosis of Dyspnea

<b>Acute dyspnea (minutes-hours)</b>
<b>Cardiac causes</b>
Ischemic heart disease
CHF exacerbation
Cardiac tamponade
<b>Pulmonary causes</b>
Upper airway obstruction (anaphylaxis, foreign body)
Airway disease (asthma, COPD exacerbation, bronchitis)
Parenchymal lung disease (ARDS, pneumonia)
Pulmonary vascular disease (PE, vasculitis)
Pleural disease (pneumothorax, tension pneumothorax)
Respiratory control (metabolic acidosis, ASA toxicity)
<b>Psychiatric</b>
Anxiety/psychosomatic
<b>Chronic dyspnea (weeks-months)</b>
<b>Cardiac causes</b>
Valvular heart disease
Decreased CO
<b>Respiratory causes</b>
Parenchymal lung disease (interstitial disease)
Pulmonary vascular disease (pulmonary HTN, vasculitis)
Pleural disease (effusion)
Airway disease – asthma, COPD
<b>Hematologic causes</b>
Severe anemia
<b>Neuromuscular and chest wall disorders</b>
Deconditioning, obesity, pregnancy, neuromuscular disease

Table 2. Differential Diagnosis of Chest Pain

(see Cardiology and Cardiovascular Surgery C4 and Emergency Medicine ER21)

<b>Nonpleuritic</b>	<b>Pleuritic</b>
<b>Pulmonary</b>	<b>Pulmonary</b>
Pneumonia	Pneumonia
PE	PE
Neoplastic	Pneumothorax
<b>Cardiac</b>	Hemothorax
MI	Neoplasm
Myocarditis/pericarditis	TB
<b>Esophageal</b>	Empyema
GERD	<b>Cardiac</b>
Spasm	Pericarditis
Esophagitis	Dressler's syndrome
Ulceration	<b>GI</b>
Achalasia	Subphrenic abscess
Neoplasm	Pancreatitis
Esophageal rupture	<b>MSK</b>
<b>Mediastinal</b>	Costochondritis
Lymphoma	Fractured rib
Thymoma	Myositis
<b>Subdiaphragmatic</b>	Herpes zoster
PUD	
Gastritis	
Biliary colic	
Pancreatitis	
<b>Vascular</b>	
Dissecting aortic aneurysm	
<b>MSK</b>	
Costochondritis	
Skin	
Breast	
Ribs	



### Most Common Causes of Chronic Cough in Healthy-Appearing Patient (cough > 3 mo with normal CXR)

- GERD
- Asthma
- Post-nasal drip
- ACEI



### Hemoptysis

- Most common cause is bronchitis
- 90% of massive hemoptysis is from the bronchial arteries
- Considered "massive" if > 600 mL/24 h



### Signs of Respiratory Distress

- Increased RR
- Nasal flaring
- Central/peripheral cyanosis
- Tracheal tug
- Inability to speak
- Accessory muscle use and tripodding
- Intercostal indrawing



Clubbing is not seen in COPD – if present, think malignancy.

Table 3. Differential Diagnosis of Hemoptysis

<b>Airway Disease</b>
Acute or chronic bronchitis
Bronchiectasis
Bronchogenic CA
Bronchial carcinoid tumour
<b>Parenchymal Disease</b>
Pneumonia
TB
Lung abscess
<b>Vascular Disease</b>
PE
Elevated pulmonary venous pressure:
LVF
Mitral stenosis
Vascular malformation
Vasculitis
Goodpasture's syndrome
Idiopathic pulmonary hemosiderosis
<b>Miscellaneous</b>
Impaired coagulation
Pulmonary endometriosis

Table 4. Differential Diagnosis of Cough

<b>Airway Irritants</b>
Inhaled smoke, dusts, fumes
Postnasal drip (upper airway cough syndrome)
<b>Aspiration</b>
Gastric contents (GERD)
Oral secretions
Foreign body
<b>Airway Disease</b>
URTI including postnasal drip and sinusitis
Acute or chronic bronchitis
Bronchiectasis
Neoplasm
External compression by node or mass lesion
Asthma
COPD
<b>Parenchymal Disease</b>
Pneumonia
Lung abscess
Interstitial lung disease
<b>CHF</b>
<b>Drug-induced (e.g. ACEI)</b>

Adapted from Principles of Pulmonary Medicine, 5th edition, SE Weinberger, Copyright (2008), with permission from Elsevier

Table 5. Differential Diagnosis of Clubbing

<b>Pulmonary</b>	<b>Gastrointestinal</b>	<b>Mediastinal</b>
Cystic fibrosis	IBD (UC, CD)	Esophageal CA
Pulmonary fibrosis	Chronic infections	Thymoma
Chronic pus in the lung (bronchiectasis, abscess, infections, etc.)	Laxative abuse	<b>Other</b>
Lung CA (primary or mets)	Polyposis	Grave's Disease
A-V fistula	Malignant tumours	Thalassemia
Solitary fibrous tumour of pleura	Cirrhosis	Other malignancies
	Hepatocellular carcinoma	Primary hypertrophic osteoarthropathy
	<b>Cardiac</b>	
	Cyanotic congenital heart disease	
	Infective endocarditis	

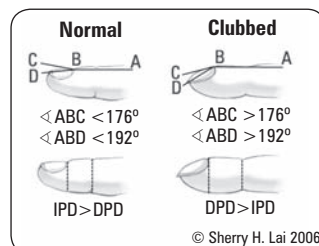


Figure 3. Three signs of clubbing

1. Profile Angle ( $ABC > 176^\circ$ )
  2. Hyponychial Angle ( $ABD > 192^\circ$ )
  3. Phalangeal Depth Ratio ( $DPD:IPD > 1$ )
- Adapted from JAMA 2001;286:341-347

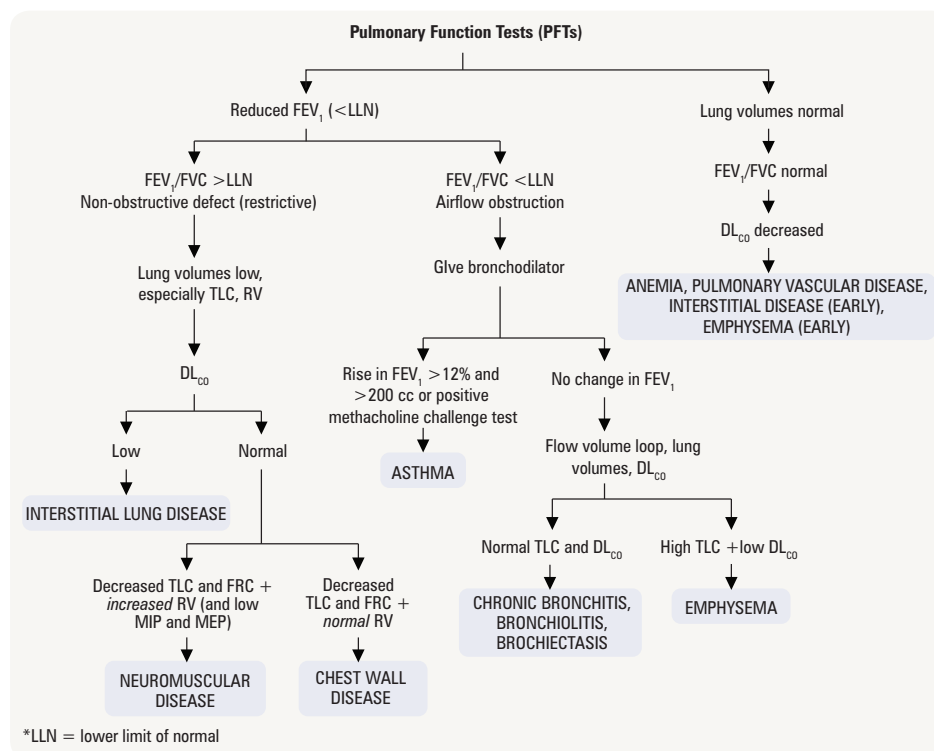
## Pulmonary Function Tests (PFTs)

- useful in differentiating the pattern of lung disease (obstructive vs. restrictive) (Table 6)
- assess lung volumes, flow rates, and diffusion capacity (see Figures 4a and 4b)
- **note:** normal values for FEV<sub>1</sub> are approximately  $\pm 20\%$  of the predicted values (for age, sex and height); ethnicity may affect predicted values

**Table 6. Comparison of Lung Flow and Volume Parameters in Obstructive vs. Restrictive Lung Disease**

	Obstructive	Restrictive
	<ul style="list-style-type: none"> <li>Decreased flow rates (most marked during expiration)</li> <li>Air trapping (increased RV/TLC)</li> <li>Hyperinflation (increased FRC, TLC)</li> </ul>	<ul style="list-style-type: none"> <li>Decreased lung compliance</li> <li>Decreased lung volumes</li> </ul>
DDx	Asthma, COPD, CF, bronchiolitis, bronchiectasis*	ILD, pleural disease, neuromuscular disease, chest wall disease
FEV <sub>1</sub> /FVC	↓	↑ or N
TLC	↑ or N	↓
RV	↑ or N	↓
RV/TLC	↑ or N	N
DL <sub>CO</sub>	↓ or N	↓ or N

\*Bronchiectasis can be obstructive or mixed



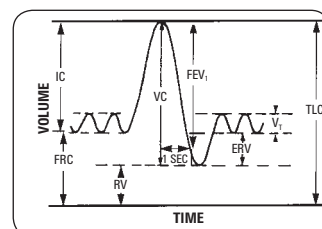
### Figure 5. Interpreting PFTs

## Chest X-Rays

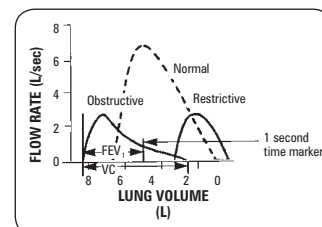
- see also [Medical Imaging](#), MI4

### Table 7. CXR Patterns and Differential Diagnosis

Pattern	Signs	Common DDx
<b>Consolidation</b> ("Airspace disease")	Air bronchogram Silhouette sign Less visible blood vessels	<u>Acute</u> : water (pulmonary edema), pus (pneumonia), blood (hemorrhage) <u>Chronic</u> : neoplasm (lymphoma), inflammatory (eosinophilic pneumonia), chronic infection (TB, fungal)
<b>Reticular</b> ("Interstitial disease")	Increased pulmonary markings Honeycombing (IPF)	ILD (IPF, collagen vascular disease, asbestos, drugs)
<b>Nodular</b>	Cavitary vs. non-cavitary	<u>Cavitary</u> : neoplasm (primary vs. metastatic lung cancer), infectious (anaerobic or Gram negative, TB, fungal), inflammatory [RA, Granulomatosis with Polyangiitis (GPA)] <u>Non-cavitary</u> : above + sarcoid, Kaposi's sarcoma (in HIV), silicosis and other pneumoconiosis



### Figure 4A. Subcompartments of lung volumes



**Figure 4B. Expiratory flow volume curves**

Adapted with permission from Elsevier. Weinberger SE.  
Principles of pulmonary medicine, 5th ed. ©2008



**Plethysmography:** involves the use of a plethysmograph (or "body box") and used to measure FRC. After a normal expiration the patient inhales against a closed mouthpiece. Resultant changes in the volume and pressure of the plethysmograph are used to calculate the volume of gas in the thorax. Useful for patients with air trapping since all air in the thoracic cavity is determined by the calculation.

**He dilution:** used to measure FRC by diluting a known amount of helium into a patient's lungs following inspiration. Since the amount of helium remains constant, FRC is determined based on the final concentration of the helium in the closed system. Only includes airspaces that communicate with the bronchial tree.

**Bronchoscopy:** a flexible or rigid bronchoscope is used for visualization of a patient's airways for diagnostic and therapeutic indications. It is used to obtain tissue washings for culture and cytology, endobronchial or transbronchial tissue biopsies, remove secretions/foreign bodies/blood, laser resections, airway stenting, etc. Mediastinal lymph nodes can also be sampled using a special bronchoscope equipped with an US probe (EBUS).



### Lung Volumes

ERV – Expiratory Reserve Volume  
 FEF – Forced Expiratory Flow Rate  
 FEV<sub>1</sub> – Forced Expiratory Volume  
           (in one second)  
 FRC – Functional Residual Capacity  
 IC – Inspiratory Capacity  
 RV – Residual Volume  
 TLC – Total Lung Capacity  
 VC – Vital Capacity  
 V<sub>T</sub> – Tidal Volume



## Arterial Blood Gases

- provides information on acid-base and oxygenation status
- see also [Nephrology](#), NP14



### Approach to Acid-Base Status

1. Is the pH acidemic (pH <7.35), alkalemic (pH >7.45), or normal (pH 7.35-7.45)?
2. What is the primary disturbance?
  - metabolic: change in  $\text{HCO}_3^-$  and pH in same direction
  - respiratory: change in  $\text{HCO}_3^-$  and pH in opposite direction
3. Is there appropriate compensation? (Table 8)
  - metabolic compensation occurs over 2-3 d reflecting altered renal  $\text{HCO}_3^-$  production and excretion
  - respiratory compensation through ventilatory control of  $\text{P}_a\text{CO}_2$  occurs immediately
  - inadequate compensation may indicate a second acid-base disorder

**Table 8. Expected Compensation for Specific Acid-Base Disorders**

Disturbance	$\text{P}_a\text{CO}_2$ (mmHg) (normal ~40)	$\text{HCO}_3^-$ (mmHg) (normal ~24)
<b>Respiratory Acidosis</b>		
Acute	↑ 10	↑ 1
Chronic	↑ 10	↑ 3
<b>Respiratory Alkalosis</b>		
Acute	↓ 10	↓ 2
Chronic	↓ 10	↓ 5
<b>Metabolic Acidosis</b>	↓ 1	↓ 1
<b>Metabolic Alkalosis</b>	↑ 5-7	↑ 10

4. If there is metabolic acidosis, what is the anion gap and osmolar gap?
  - anion gap =  $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$ ; normal ≤10-15 mmol/L
  - osmolar gap = measured osmolarity – calculated osmolarity = measured –  $(2[\text{Na}^+] + \text{glucose} + \text{urea})$ ; normal ≤10
5. If anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
  - if not, consider a mixed metabolic picture

**Table 9. Differential Diagnosis of Respiratory Acidosis**

*Increased  $\text{P}_a\text{CO}_2$  secondary to hypoventilation*

#### Respiratory centre depression (decreased RR)

Drugs (anesthesia, sedatives, narcotics)  
Trauma  
Increased ICP  
Encephalitis  
Stroke  
Central apnea  
Supplemental  $\text{O}_2$  in chronic  $\text{CO}_2$  retainers (i.e. COPD)

#### Neuromuscular disorders (decreased vital capacity)

Myasthenia gravis  
Guillain-Barré syndrome  
Poliomyelitis  
Muscular dystrophies  
ALS  
Myopathies  
Chest wall disease (obesity, kyphoscoliosis)

#### Airway obstruction (asthma, COPD)

#### Parenchymal disease

COPD  
Pulmonary edema  
Pneumothorax  
Pneumonia  
ILD (late stage)  
ARDS

#### Mechanical hypoventilation (inadequate mechanical ventilation)

**Table 10. Differential Diagnosis of Respiratory Alkalosis**

*Decreased  $\text{P}_a\text{CO}_2$  secondary to hyperventilation*

#### Hypoxemia

Pulmonary disease (pneumonia, edema, PE, interstitial fibrosis)  
Severe anemia  
Heart failure  
High altitude

#### Respiratory centre stimulation

CNS disorders  
Hepatic failure  
Gram-negative sepsis  
Drugs (ASA, progesterone, theophylline, catecholamines, psychotropics)  
Pregnancy  
Anxiety  
Pain

#### Mechanical hyperventilation (excessive mechanical ventilation)



### Diffusion Capacity for Carbon Monoxide ( $\text{DL}_{\text{CO}}$ )

#### $\text{DL}_{\text{CO}}$ decreases with:

- Decreased surface area (e.g. emphysema)
- Decreased hemoglobin
- Interstitial lung disease
- Pulmonary vascular disease

#### $\text{DL}_{\text{CO}}$ increases with:

- Asthma
- Pulmonary hemorrhage
- Polycythemia
- Increased pulmonary blood volume



OG = measured osmolarity – calculated osmolarity; for calculated osmolarity think "2 salts and a sticky BUN" ( $2\text{Na}^+ + \text{glucose} + \text{urea}$ )



Note: Mixed acid-base disturbances can still have a "normal pH"



### Ventilation Failure: Think "Can't Breathe" vs. "Won't Breathe" (increased $\text{P}_a\text{CO}_2$ )

#### Can't Breathe

- Neuromuscular disorders
- Airway obstruction
- Parenchymal disease

#### Won't Breathe

- Respiratory centre depression
- Hypothyroidism
- Sleep apnea (central)



### Anion Gap Metabolic Acidosis

#### KARME

Ketoacidosis  
ASA  
Renal failure (uremia)  
Methanol  
Ethylene glycol  
Lactic acidosis

#### MUDPILES

Methanol  
Uremia  
Diabetic ketoacidosis/starvation ketoacidosis  
Phenformin/Paraldehyde  
Isoniazid, Iron, Ibuprofen  
Lactate  
Ethylene glycol  
Salicylates  
Cyanide, Carbon dioxide  
Alcoholic ketoacidosis  
Toluene, Theophylline



Acidosis ↔ Hyperkalemia  
Alkalosis ↔ Hypokalemia

- see [Nephrology](#), NP14 for differential diagnosis of metabolic acidosis and alkalosis





## Approach to Hypoxemia

1.  $P_aO_2$ : What is the arterial oxygen tension? (Measured by ABG. Normal = 95-100 mmHg)
2. A-a $DO_2$ : What is the oxygen gradient between alveoli and pulmonary capillaries? (Calculate. See sidebar. Normal <15 mmHg but increases with age)
3. What is the cause of the hypoxemia? (see Figure 7)

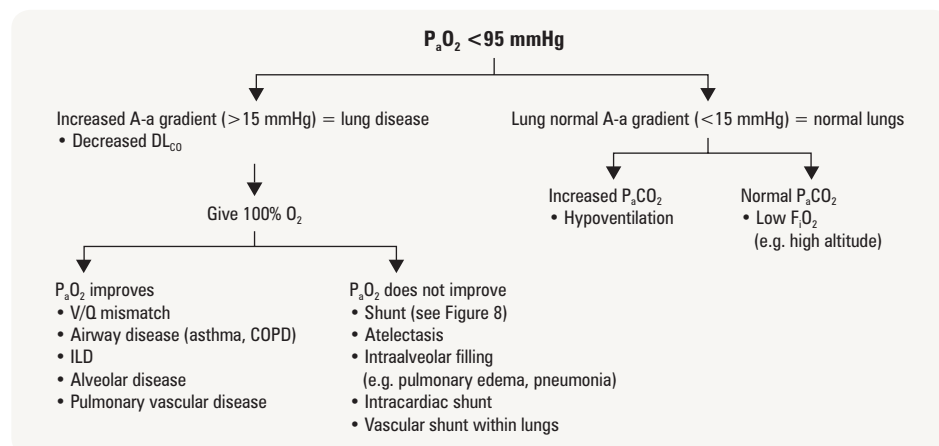


Figure 7. Approach to hypoxemia

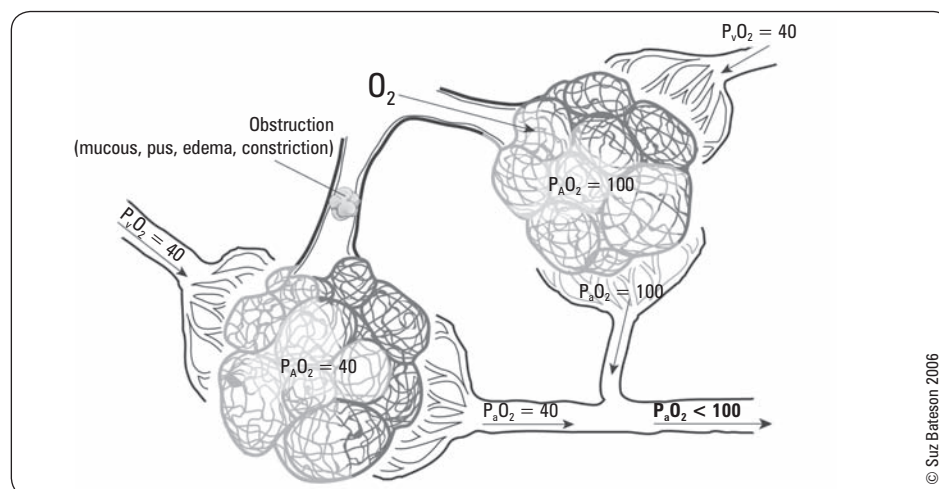


Figure 8. Pathophysiology of shunt



### ABG Normal Values

pH 7.35-7.45  
 $HCO_3^-$  22-26 mEq/L  
 $P_aCO_2$  35-45 mm Hg  
 $P_aO_2$  80-100 mm Hg



### A-a $DO_2$ Gradient Calculation

$= P_aO_2 \text{ (alveolar)} - P_aO_2 \text{ (arterial)}$   
 $= [F_iO_2 (P_{atm} - PH_2O) - (P_aCO_2/RQ)] - P_aO_2$



### At Sea Level on Room Air

$FiO_2 = 0.21$   
 $P_{atm} = 760$  mmHg  
 $PH_2O = 47$  mmHg  
 $RQ = 0.8$   
 Thus, A-a $DO_2$  Gradient on Room Air  
 $A-aDO_2 = \{150 - 1.25 (P_aCO_2)\} - P_aO_2$

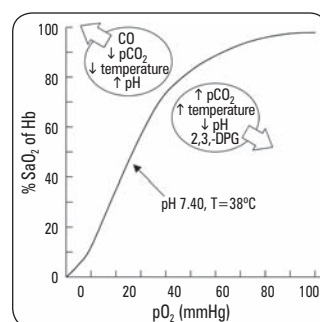


Figure 6. Oxygen-Hb dissociation curve



### Pulmonary Shunt

Occurs when the capillary networks of the alveoli are perfused, yet there is a lack of adequate ventilation (and thus oxygenation) in that alveolus or group of alveoli. Thus this blood enters the pulmonary venous system without being oxygenated.



### Factors that shift the Oxygen-Hb Dissociation curve to the right

"CADET, face right!"

$CO_2$   
 Acid  
 2,3-DPG  
 Exercise  
 Temperature

## Diseases of Airway Obstruction

### Pneumonia

- see [Infectious Diseases](#), ID8



### Asthma

- see also [Family Medicine](#), FM16 and [Pediatrics](#), P94



### Definition

- chronic inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
- associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli

### Epidemiology

- common, 7-10% of adults, 10-15% of children
- most children with asthma significantly improve in adolescence
- often family history of atopy (asthma, allergic rhinitis, eczema)
- occupational asthma (organic allergies, isocyanates, animals, etc.)

## Pathophysiology

- airway obstruction  $\rightarrow$  V/Q mismatch  $\rightarrow$  hypoxemia  $\rightarrow$   $\uparrow$  ventilation  $\rightarrow$   $\downarrow$   $P_a\text{CO}_2 \rightarrow \uparrow$  pH and muscle fatigue  $\rightarrow$   $\downarrow$  ventilation,  $\uparrow$   $P_a\text{CO}_2/\downarrow$  pH

## Triggers

- URTIs, allergens (pet dander, house dust, moulds), irritants (cigarette smoke, air pollution), drugs (NSAIDs,  $\beta$ -blockers), preservatives (sulphites, MSG), other (emotion/anxiety, cold air, exercise, GERD)

## Signs and Symptoms

- dyspnea, wheezing, chest tightness, cough (especially nocturnal), sputum
- symptoms can be paroxysmal or persistent
- signs of respiratory distress (see sidebar R3)
- pulsus paradoxus

**Table 11. Criteria for Determining if Asthma is Well Controlled**

Daytime symptoms <4 d/wk	No asthma-related absence from work/school
Night-time symptoms <1 night/wk	$\beta_2$ -agonist use <4 times/wk
Physical activity normal	FEV <sub>1</sub> or PEF >90% of personal best
Exacerbations mild, infrequent	PEF diurnal variation <10-15%

Adapted from Can Respir J 2012; 19:127-164

## Investigations

- O<sub>2</sub> saturation
- ABGs (consider in acute exacerbation, along with peak flows, in Emergency Department)
  - decreased  $P_a\text{O}_2$  during attack (V/Q mismatch)
    - decreased  $P_a\text{CO}_2$  in mild asthma (hyperventilation)
    - normal or increased  $P_a\text{CO}_2$  is an ominous sign: patient is no longer able to hyperventilate (worsened airway obstruction or respiratory muscle fatigue)
- PFTs (do when stable) (see Table 12)

**Table 12. Pulmonary Function Criteria for Diagnosis of Asthma**

Preferred Measurement	Alternative Measurements
<b>Spirometry Showing Reversible Airway Obstruction</b> (1) $\downarrow$ FEV <sub>1</sub> /FVC below lower limit of normal (<0.75 to 0.8 in adults, <0.8-0.9 in children age 6+)	<b>Peak Expiratory Flow Variability</b> (1) $\uparrow$ in PEF after a bronchodilator or course of controller therapy <ul style="list-style-type: none"> <li>Adults: PEF <math>\uparrow</math> 60 L/min (min. 20%) OR Diurnal variation &gt;8% for twice daily readings (20% for multiple daily readings)</li> <li>Children age 6+: PEF <math>\uparrow</math> 20%</li> </ul>
AND  (2) $\uparrow$ FEV <sub>1</sub> $\geq$ 12% (min. 200 mL in adults) after bronchodilator or controller therapy	<b>Positive Challenge Test</b> (1) Methacholine challenge: PC <sub>20</sub> <4 mg/mL (4-16 mg/mL is borderline; >16 mg/mL is negative) OR (2) Post-exercise: $\downarrow$ FEV <sub>1</sub> $\geq$ 10-15%

Adapted from Can Respir J 2012; 19:127-164

## Treatment

- environment: avoid triggers
- patient education: features of the disease, goals of treatment, self-monitoring
- pharmacological
  - symptomatic relief in acute episodes: short-acting  $\beta_2$ -agonist, anticholinergic bronchodilators, oral steroids, addition of a long acting  $\beta_2$ -agonist
  - long-term prevention: inhaled/oral corticosteroids, anti-allergic agents, long-acting  $\beta_2$ -agonists, methylxanthine, LTRA, anti-IgE antibodies (e.g. Xolair®)



### Airway Obstruction (decreased FEV<sub>1</sub>)

- Asthma
- COPD (chronic bronchitis, emphysema)
- Bronchiectasis
- Cystic fibrosis



### Red Flags

Severe tachypnea/tachycardia, respiratory muscle fatigue, diminished expiratory effort, cyanosis, silent chest, decreased LOC.



Central cyanosis is not detectable until SaO<sub>2</sub> is <85%. It is more easily detected in polycythemia and less readily detectable in anemia.



### Aspirin®-Exacerbated Respiratory Disease (AERD, formerly Samter's Triad)

- Asthma
- ASA/NSAID sensitivity
- Nasal polyps
- Chronic hyperplastic sinusitis



### Asthma Action Plan

Is a written plan developed by patients and their physicians which includes signs and symptoms for patients to recognize their current level of respiratory distress (denoted as 'green', 'yellow' or 'red/emergency' zones) and the personalized treatment options for each zone.

## Guidelines for Asthma Management

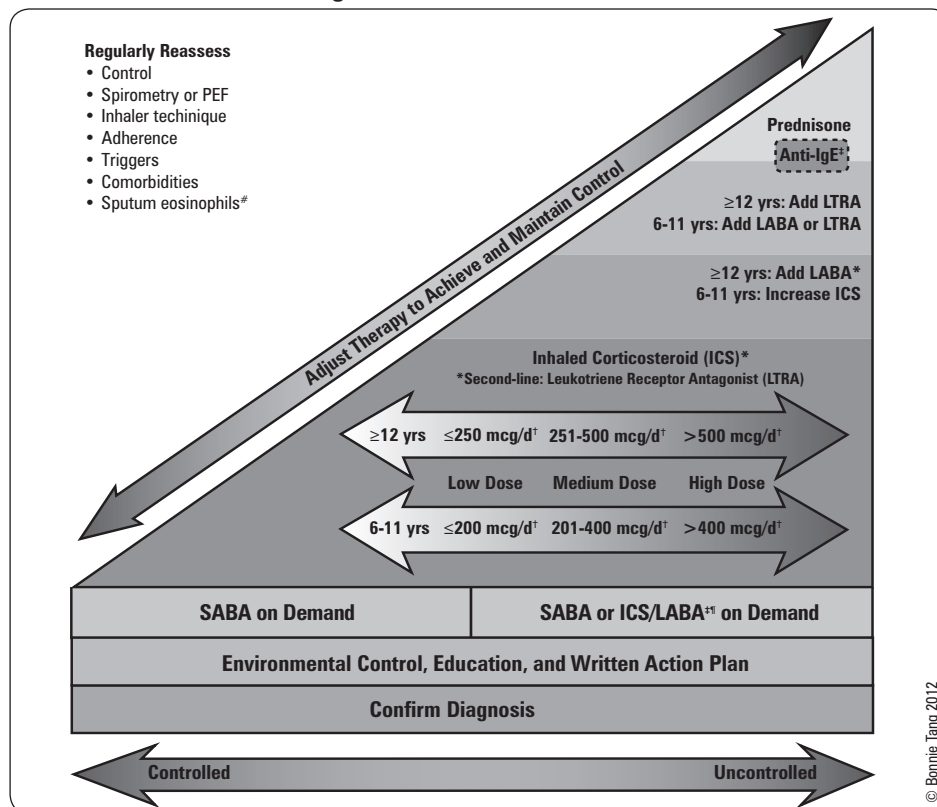


Figure 9. Guidelines for asthma management

†HFA Beclothemason or equivalent; \*Second-line: LTRA; ‡Approved for 12 yr and over; †Using a formulation approved for use as a reliever; #In adults 18 yr and older with moderate to severe asthma

Adapted from Can Respir J 2012;19:127-164

Emergency Management of Asthma (see also [Emergency Medicine](#), ER30)

- inhaled  $\beta_2$ -agonist first line (MDI route and spacer device recommended)
- systemic steroids (PO or IV, if severe)
- add anticholinergic therapy  $\pm$  magnesium sulphate
- rapid sequence intubation in life-threatening cases (plus 100% O<sub>2</sub>, monitors, IV access)
- SC/IV adrenaline, IV salbutamol if unresponsive
- corticosteroid therapy at discharge

## Chronic Obstructive Pulmonary Disease (COPD)

- see also [Family Medicine](#), FM16

## Definition

- progressive, and irreversible condition of the lung characterized by chronic obstruction to airflow with many patients having periodic exacerbations, gas trapping, lung hyperinflation and weight loss
- 2 subtypes (chronic bronchitis or emphysema): usually coexist to variable degrees
- gradual decrease in FEV<sub>1</sub> over time with episodes of acute exacerbations

Table 13. Clinical and Pathologic Features of COPD\*

Chronic Bronchitis	Emphysema
<b>Defined clinically:</b> Productive cough on most days for at least 3 consecutive months in 2 successive years Obstruction is due to narrowing of the airway lumen by mucosal thickening and excess mucus	<b>Defined pathologically:</b> Dilation and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse, and air trapping
	<b>2 types:</b> 1) <b>Centriacinar</b> (respiratory bronchioles predominantly affected) • Typical form seen in smokers, primarily affects upper lung zones 2) <b>Panacinar</b> (respiratory bronchioles, alveolar ducts, and alveolar sacs affected) • Accounts for about 1% of emphysema cases • $\alpha_1$ -antitrypsin deficiency, primarily affects lower lobes

\*Note that both chronic bronchitis and emphysema can exist without obstruction. Only if obstruction is also present is it termed COPD



Consider LABA for night-time symptoms.



## LTRA in Addition to Usual Care for Acute Asthma in Adults and Children

Cochrane DB Syst Rev 2012;CD006100

**Purpose:** To determine if the addition of LTRA is beneficial to patients with acute asthma receiving inhaled bronchodilators and systemic corticosteroids.

**Methods:** RCTs in Cochrane Airway Group's Specialised Register of trials that compared LTRA and standard acute asthma versus placebo and standard care in people with acute asthma of any age were included.

**Results:** 8 trials, 1470 adults and 470 children. For oral treatment, no significant difference between LTRAs and control in hospital admission (RR 0.86; 95%CI 0.21 to 3.52) or requirement for additional care (RR 0.87; 95%CI 0.60 to 1.68). LTRAs improved FEV<sub>1</sub> in adults (mean difference 0.08; 95%CI 0.01 to 0.14) but not in children. No significant difference in adverse events between LTRAs and control (RR 0.81; 95%CI 0.22 to 2.99). Similar results were found for intravenous treatment

**Conclusions:** Currently, there is no evidence to support routine use of LTRAs in acute asthma.



## Natural Progression of COPD

- 40s** Chronic productive cough, wheezing occasionally
- 50s** 1<sup>st</sup> acute chest illness
- 60s** Dyspnea on exertion, increasing sputum, more frequent exacerbations
- Late Stage** Hypoxemia with cyanosis, polycythemia, hypercapnia (morning headache), cor pulmonale, weight loss



Remember, first line therapy for COPD is smoking cessation

**Risk Factors**

- smoking is #1 risk factor
- others:
  - environmental: air pollution, occupational exposure, exposure to wood smoke or other biomass fuel for cooking
  - treatable factors:  $\alpha_1$ -antitrypsin deficiency, bronchial hyperactivity
  - demographic factors: age, family history, male sex, history of childhood respiratory infections, low socioeconomic status

**Signs and Symptoms****Table 14. Clinical Presentation and Investigations for Chronic Bronchitis and Emphysema**

	Symptoms	Signs	Investigations
<b>Bronchitis (Blue Bloater*)</b>	Chronic productive cough Purulent sputum Hemoptysis Mild dyspnea initially	Cyanosis (2° to hypoxemia and hypercapnia) Peripheral edema from RVF (cor pulmonale) Crackles, wheezes Prolonged expiration if obstructive Frequently obese	<b>PFT:</b> ↓ FEV <sub>1</sub> , ↓ FEV <sub>1</sub> /FVC N TLC, ↓ or N DL <sub>CO</sub> <b>CXR:</b> AP diameter normal ↑ bronchovascular markings Enlarged heart with cor pulmonale
<b>Emphysema (Pink Puffer*)</b>	Dyspnea (± exertion) Minimal cough Tachypnea Decreased exercise tolerance	Pink skin Pursed-lip breathing Accessory muscle use Cachectic appearance due to anorexia and increased work of breathing Hyperinflation/barrel chest, hyperresonant percussion Decreased breath sounds Decreased diaphragmatic excursion	<b>PFT:</b> ↓ FEV <sub>1</sub> , ↓ FEV <sub>1</sub> /FVC ↑ TLC (hyperinflation) ↑ RV (gas trapping) ↓ DL <sub>CO</sub> <b>CXR:</b> ↑ AP diameter Flat hemidiaphragm (on lateral CXR) ↓ heart shadow ↑ retrosternal space Bullae ↓ peripheral vascular markings

\*Note that the distinction between "blue bloaters" and "pink puffers" is more of historical than practical interest as most COPD patients have elements of both

**Table 15. Treatment of Stable COPD**

Treatment	Details
<b>PROLONG SURVIVAL</b>	
Smoking cessation	Nicotine replacement, bupropion, varenicline
Vaccination	Influenza, pneumococcal vaccine
Home oxygen	Prevents cor pulmonale and decreases mortality if used >15h/d; indicated if (1) P <sub>a</sub> O <sub>2</sub> <55 mmHg or (2) <60 mmHg with cor pulmonale or polycythemia
<b>SYMPTOMATIC RELIEF</b> (no mortality benefit)	
Bronchodilators (mainstay of current drug therapy, used in combination)	<p>Short-acting anticholinergics (e.g. ipratropium bromide) and short-acting <math>\beta_2</math>-agonists (e.g. salbutamol, terbutaline)</p> <ul style="list-style-type: none"> <li>• SABAs: rapid onset but significant side effects at high doses (e.g. hypokalemia)</li> <li>• Short-acting anticholinergics more effective than SABAs with fewer side effects but slower onset; take regularly rather than PRN</li> </ul> <p>LABAs (e.g. salmeterol, formoterol, indacaterol) and long-acting anticholinergics (e.g. tiotropium bromide, glycopyrronium bromide)</p> <ul style="list-style-type: none"> <li>• More sustained effects for moderate to severe COPD</li> </ul> <p>Inhaled corticosteroid (ICS) + LABA combination (e.g. Advair®: fluticasone + salmeterol, Symbicort®: budesonide + formoterol)</p> <ul style="list-style-type: none"> <li>• ICS/LABA increases effectiveness vs. LABA alone</li> </ul> <p>Theophylline: weak bronchodilator; limited evidence to suggest combination with bronchodilator</p> <ul style="list-style-type: none"> <li>• Side effects: nervous tremor, nausea/vomiting/diarrhea, tachycardia, arrhythmias, sleep changes</li> </ul> <p>PDE4 inhibitor: roflumilast (Daxas®) – weak bronchodilator</p>
Corticosteroids	ICS monotherapy is contraindicated and ICS should only be used with a LABA in combination in patients with a history of exacerbations COPD airways are usually inflamed but often not responsive to steroids, therefore avoid chronic systemic glucocorticoids (although oral steroids are very important when treating exacerbations)
Surgical	Lung volume reduction surgery (resection of emphysematous parts of lung, associated with higher mortality if FEV <sub>1</sub> <20%), lung transplant Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance
Other	Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance

 **$\alpha_1$ -Antitrypsin Deficiency**

Inherited disorder of defective production of  $\alpha_1$ -antitrypsin, a protein produced by hepatocytes. Acts in the alveolar tissue by inhibiting the action of proteases from destroying alveolar tissue. When deficient, proteases can destroy lung alveoli resulting in emphysema.

**CO<sub>2</sub> Retainers**

On ABG, retainers have chronically elevated CO<sub>2</sub> levels with a normal pH. Maintain O<sub>2</sub> Sat between 88-92% to prevent Haldane effect and decreased respiratory drive.


**Pulmonary Embolism in Patients with Unexplained Exacerbation of COPD: Prevalence and Risk Factors**

*Ann Intern Med* 2006;144:390-396

**Study:** Prospective cohort study of 211 patients with COPD (all current and former smokers) admitted to hospital for severe COPD exacerbation of unknown origin.

**Measurements:** All patients received spiral CT angiogram (CTA) and venous compression ultrasonography of both legs.

**Results:** 25% of patients met diagnostic criteria for PE (+ CTA or + U/S).

**Conclusions:** Prevalence of PE in patients hospitalized for COPD exacerbation of unknown origin is 25%. Therefore, all patients presenting to hospital with COPD exacerbation without obvious cause require PE workup (leg dopplers or CTA – decision of which to use depends on pre-test probability of the patient).


**Non-invasive Positive Pressure Ventilation for Treatment of Respiratory Failure due to Exacerbations of COPD**

*Cochrane DB Syst Rev* 2004;CD004104

**Study:** Cochrane Systematic Review. 14 RCTs.

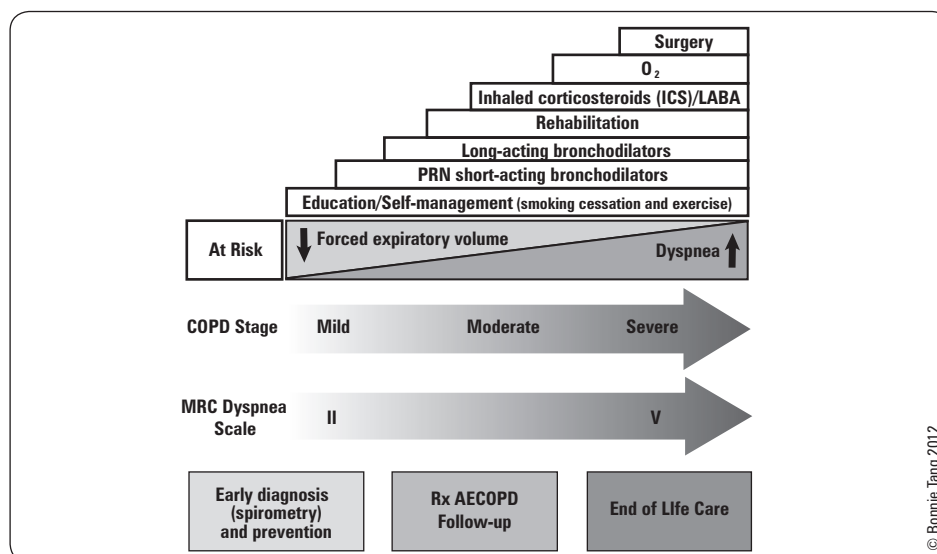
**Population:** 758 adult patients with COPD and acute respiratory failure due to COPD exacerbation.

**Intervention:** Usual medical care (UMC) and Non-invasive positive ventilation (NPPV) versus UMC alone.

**Primary Outcome:** Treatment failure, mortality, and tracheal intubation.

**Results:** The risks for all primary outcomes were reduced with NPPV use: treatment failure (RR 0.48); mortality (RR 0.52); and intubation use (RR 0.61). Length of hospital stay was a significant mean 3.24 d shorter, but no difference between ICU length of stay. There is a small and significant improvement in pH (weight mean difference (WMD)=0.04), P<sub>a</sub>CO<sub>2</sub> (WMD=0.40 kPa), and respiratory rate (WMD=-3.08 bpm) within 1 h post-treatment with NPPV. Complications associated with treatment were reduced in the NPPV treatment arm (RR 0.38).

**Conclusion:** For patients in respiratory failure due to a COPD exacerbation, NPPV is effective in reducing treatment failure, mortality, and need for intubation when used as a first time treatment adjunct to UMC.



**Figure 10. Guidelines for COPD management**

Adapted from Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease. Can Respir J 2008;(Suppl A):15

### Acute Exacerbations of COPD

#### • definition

- sustained (>24-48 h) worsening of dyspnea, cough, or sputum production leading to an increased use of medications

#### • etiology: viral URTI, bacteria, air pollution, CHF, PE, MI must be considered

#### • management

- ABCs, consider assisted ventilation if decreasing LOC or poor ABGs
- O<sub>2</sub>: target 88-92% SaO<sub>2</sub> for CO<sub>2</sub> retainers
- bronchodilators by MDI with spacer or nebulizer
  - ♦ SABA + anticholinergic, e.g. salbutamol and ipratropium bromide via nebulizers x 3 back-to-back
- systemic corticosteroids: IV solumedrol or oral prednisone
- antibiotics if purulent sputum
  - ♦ simple exacerbation (no risk factors): amoxicillin, 2<sup>nd</sup> or 3<sup>rd</sup> generation cephalosporin, macrolide, or TMP/SMX
  - ♦ complicated exacerbation (one of: FEV<sub>1</sub> ≤50% predicted, ≥4 exacerbations per year, ischemic heart disease, home O<sub>2</sub> use, chronic oral steroid use): fluoroquinolone or β-lactam + β-lactamase inhibitor (amoxicillin/clavulanate)
- post exacerbation: rehabilitation with general conditioning to improve exercise tolerance

#### • ICU admission

- for life threatening exacerbations
- ventilatory support
  - ♦ non-invasive: NPPV, BiPAP
  - ♦ conventional mechanical ventilation

### Prognosis in COPD

#### • prognostic factors

- level of dyspnea is the single best predictor
- development of complications, e.g. hypoxemia or cor pulmonale

#### • 5-yr survival

- FEV<sub>1</sub> <1 L = 50%
- FEV<sub>1</sub> <0.75 L = 33%

#### • BODE index for risk of death in COPD

- greater score = higher probability the patient will die from COPD; score can also be used to predict hospitalization
- 10 point index consisting of four factors:
  - ♦ Body mass index (BMI): <21 (+1 point)
  - ♦ Obstruction (FEV<sub>1</sub>): 50-64% (+1), 36-49% (+2), <35% (+3)
  - ♦ Dyspnea (MRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
  - ♦ Exercise capacity (6 minute walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)



Remember to step down therapy to lowest doses which control symptoms/signs of bronchoconstriction.



#### Complications of COPD

- Polycythemia 2° to hypoxemia
- Chronic hypoxemia
- Pulmonary HTN from vasoconstriction
- Cor pulmonale
- Pneumothorax due to rupture of emphysematous bullae



#### Influenza Vaccine for Patients with Chronic Obstructive Pulmonary Disease

Cochrane DB Syst Rev 2006;1:CD002733

**Study:** Cochrane Systematic Review. 11 RCTs included, 6 specifically in COPD patients.

**Population:** 6 of the studies were done on COPD patients in particular, while the others were on elderly and high-risk individuals. Asthma patients were excluded.

**Intervention:** Live or inactivated virus vaccines vs. placebo.

**Outcome:** Exacerbation rates, hospitalizations, mortality, lung function and adverse effects.

**Results:** In patients with COPD, inactivated vaccine correlated with fewer exacerbations per vaccinated subject than placebo (Weighted mean difference (WMD) -0.37, 95% 0.64 to -0.11). Inactivated vaccine resulted in fewer influenza-related infections than placebo (WMD 0.19, 95% 0.07-0.49). There was also an increased risk of local mild, transient adverse reactions with the vaccine.

**Conclusions:** There appears to be a reduction in influenza related infections, as well as exacerbations in patients with COPD receiving the vaccine.



#### Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Cochrane DB Syst Rev 2009;1:CD001288

**Study:** Cochrane Systematic Review. 10 RCTs contributed data for analysis.

**Population:** 1051 total patients with COPD experiencing acute exacerbations.

**Intervention:** Oral or parenteral corticosteroids vs. placebo.

**Outcome:** Rate of treatment failure, length of hospitalization, FEV<sub>1</sub>.

**Results:** Patients receiving corticosteroids experienced fewer treatment failures than placebo (OR 0.50, 95% 0.36-0.69). The length of stay in hospital was shorter in patients receiving steroids (-1.22 d, 95% -2.26 to -0.18). There was also an improvement in FEV<sub>1</sub> at 72 h (140 mL, 95% 90-190) and at end of treatment (up to 15 d) (80 mL, 95% 10-160). The risk of hypoglycemia was increased (OR 4.95, 95% 2.47-9.91).

**Conclusions:** There appears to be a reduction in rate of treatment failure, reduced length of hospitalization and improved FEV<sub>1</sub> in patients receiving corticosteroid treatment for an acute exacerbation of COPD. However, there is also an increase in significant adverse effects. The ideal length of treatment remains controversial.



## Bronchiectasis

### Definition

- irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently infected mucus
- usually affects medium sized airways
- P. aeruginosa* is the most common pathogen; *S. aureus*, *H. influenzae* and nontuberculous mycobacteria also common

**Table 16. Etiology and Pathophysiology of Bronchiectasis**

Obstruction	Post-infection (results in dilatation of bronchial walls)	Impaired defenses (leads to interference of drainage, chronic infections and inflammation)
Tumour	Pneumonia	Hypogammaglobulinemia
Foreign body	TB	CF
Thick mucus	Measles	Defective leukocyte function
	Pertussis	Ciliary dysfunction (Kartagener's syndrome: bronchiectasis, sinusitis, situs inversus)
	Allergic bronchopulmonary aspergillosis	
	MAC ( <i>Mycobacteria avium</i> complex)	

### Signs and Symptoms

- chronic cough, purulent sputum (but 10-20% have dry cough), hemoptysis (can be massive), recurrent pneumonia, local crackles (inspiratory and expiratory), wheezes
- clubbing
- may be difficult to differentiate from chronic bronchitis

### Investigations

- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
  - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
  - specific: "tram tracking" – parallel narrow lines radiating from hilum, cystic spaces, honeycomb like structures
- high-resolution thoracic CT (diagnostic, gold standard):
  - 87-97% sensitivity, 93-100% specificity
  - "signet ring": dilated bronchi with thickened walls where diameter bronchus > diameter of accompanying artery
- sputum cultures (routine + AFB)
- serum Ig levels
- sweat chloride if cystic fibrosis suspected (upper zone predominant)

### Treatment

- vaccination: influenza and Pneumovax®
- antibiotics (oral, IV, inhaled): routinely used for mild exacerbations, driven by sputum sensitivity; macrolides may be used chronically for an anti-inflammatory effect
- inhaled corticosteroids: decrease inflammation and improve FEV<sub>1</sub>
- oral corticosteroids for acute, major exacerbations
- chest physiotherapy, breathing exercises, physical exercise
- pulmonary resection: in selected cases with focal bronchiectasis

## Cystic Fibrosis (CF)

- see also [Pediatrics](#), P95

### Pathophysiology

- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, skin, reproductive organs) and blockage of secretory ducts

### Clinical Features

- results in severe lung disease, pancreatic insufficiency, diabetes and azoospermia
- other manifestations: meconium ileus in infancy, distal ileal obstruction in adults, sinusitis, liver disease
- chronic lung infections
  - S. aureus*: early
  - P. aeruginosa*: most common
  - B. cepacia*: worse prognosis but less common
  - Aspergillus fumigatus*

### Investigations

- sweat chloride test
  - increased concentrations of NaCl and K<sup>+</sup> ([Cl<sup>-</sup>] >60 mmol/L is diagnostic in children)
  - heterozygotes have normal sweat tests (and no symptoms)
- PFTs
  - early: airflow limitation in small airways
  - late: severe airflow hyperinflation, gas trapping, decreased DL<sub>CO</sub> (very late)



Usually presents in childhood as recurrent lung infections that become persistent and chronic.



- ABGs
  - hypoxemia, hypercapnia later in disease with eventual respiratory failure and cor pulmonale
- CXR
  - hyperinflation, increased pulmonary markings (especially upper lobes)

### Treatment

- chest physiotherapy and postural drainage
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity), hypertonic saline DNase
- inhaled tobramycin
- antibiotics (e.g. ciprofloxacin)
- lung transplant
- pancreatic enzyme replacements

### Prognosis

- depends on: infections (cepacia colonization), FEV<sub>1</sub>, acute pulmonary exacerbations, lung transplant vs. non-lung transplant

## Interstitial Lung Disease (ILD)



### Pathophysiology

- inflammatory and/or fibrosing process in the alveolar walls → distortion and destruction of normal alveoli and microvasculature
- typically associated with:
  - lung restriction (decrease in TLC and VC)
  - decreased lung compliance (increased or normal FEV<sub>1</sub>/FVC)
  - impaired diffusion (decreased DL<sub>CO</sub>)
  - hypoxemia due to V/Q mismatch (usually without hypercapnia until end stage)
  - pulmonary HTN and cor pulmonale occur with advanced disease secondary to hypoxemia and blood vessel destruction

### Etiology

- >100 known disorders can cause ILD
- majority due to unknown agents or cause

Table 17. Interstitial Lung Diseases

UNKNOWN ETIOLOGY		
Idiopathic interstitial pneumonias	Sarcoidosis	
UIP (usual interstitial pneumonia aka IPF)	Langerhans-cell histiocytosis (eosinophilic granuloma)	
NSIP (non-specific interstitial pneumonia)	Lymphangioleiomyomatosis	
LIP (lymphocytic interstitial pneumonia)	Pulmonary infiltrates with eosinophilia (PIE syndromes)	
COP (cryptogenic organizing pneumonia aka BOOP)		
KNOWN ETIOLOGY		
<b>ILD Associated With Systemic Rheumatic Disorders</b>	<b>ILD Associated With Drugs or Treatments</b>	<b>Inherited Disorders</b>
Scleroderma	Antibiotics (nitrofurantoin)	Familial IPF
Rheumatoid arthritis	Anti-inflammatory agents (methotrexate)	Telomerase mutations
SLE	Cardiovascular drugs (amiodarone)	Neurofibromatosis
Polymyositis/dermatomyositis	Antineoplastic agents (chemotherapy agents)	Tuberous sclerosis
Mixed connective tissue disease	Illicit drugs	Gaucher's disease
<b>Environment/Occupation Associated ILD</b>	Radiation	<b>Alveolar Filling Disorders</b>
Hypersensitivity pneumonitis (usually organic antigen)	<b>ILD Associated With Pulmonary Vasculitis</b>	Chronic eosinophilic pneumonia
Farmer's lung	Granulomatosis with Polyangiitis (GPA)	Pulmonary alveolar proteinosis
Air conditioner/humidifier lung	Goodpasture's syndrome	
Bird breeder's lung	Idiopathic pulmonary hemosiderosis	
Pneumoconioses (inorganic dust)		
Silicosis		
Asbestosis		
Coal workers' pneumoconiosis		
Chronic Beryllium Disease		
Pneumonitis from Gases/fumes/vapour		



In ILD think  
**FASSTEN** and **BAD RASH**

#### Upper Lung Disease (FASTEN)

**Farmer's lung** (hypersensitivity pneumonitis)  
**Ankylosing spondylitis**  
**Sarcoidosis**  
**Silicosis**  
**TB**  
**Eosinophilic granuloma** (Langerhans cell histiocytosis)  
**Neurofibromatosis**

#### Lower Lung Disease (BAD RASH)

**Bronchiolitis obliterans** with organizing pneumonia (BOOP)  
**Asbestosis**  
**Drugs** (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs)  
**Rheumatologic disease**  
**Aspiration**  
**Scleroderma**  
**Hamman Rich** (acute interstitial pneumonia) and IPF

## Signs and Symptoms

- SOB, especially on exertion
- nonproductive cough
- crackles (dry, fine, end-inspiratory)
- clubbing (especially in IPF and asbestosis)
- features of cor pulmonale
- note that signs and symptoms vary with underlying disease process
  - e.g. sarcoidosis is seldom associated with crackles and clubbing

## Investigations

- CXR/high resolution CT (see also [Medical Imaging](#), MI7)
  - usually decreased lung volumes
  - reticular, nodular, or reticulonodular pattern (nodular <3 mm)
  - hilar/mediastinal adenopathy (especially in sarcoidosis)
- PFTs
  - restrictive pattern: decreased lung volumes and compliance
  - normal or increased FEV<sub>1</sub>/FVC (>70-80%), i.e. flow rates are often normal or high when corrected for absolute lung volume
  - DL<sub>CO</sub> decreased due to V/Q mismatch less surface area for gas exchange ± pulmonary vascular disease
- ABGs
  - with progression of disease, hypoxemia and respiratory alkalosis may be present
- other
  - bronchoscopy, bronchoalveolar lavage, lung biopsy
  - ESR, ANA (lupus), RF (RA), serum-precipitating antibodies to inhaled organic antigens (hypersensitivity pneumonitis), c-ANCA (GPA), anti-GBM (Goodpasture's)



The CXR can be normal in up to 15% of patients with interstitial lung disease.



## Unknown Etiologic Agents

### USUAL INTERSTITIAL PNEUMONIA (UIP) aka IDIOPATHIC PULMONARY FIBROSIS (IPF) (aka CRYPTOGENIC FIBROSING ALVEOLITIS)

#### Definition

- a progressive, irreversible condition characterized by fibrosis of lung parenchyma with no known cause
  - chest CT usually shows honeycomb lung, lung biopsy shows UIP (usual interstitial pneumonia) pattern
    - ♦ commonly presents over age 50, incidence rises with age; males > females
- DDx:
  - other idiopathic interstitial pneumonia, especially NSIP, but also COP and:
    - ♦ desquamative interstitial pneumonitis (DIP)
    - ♦ lymphocytic interstitial pneumonitis (LIP): usually 2° to immune conditions such as HIV (mostly in children), Sjögren's (now considered to be a hematological malignancy in most adult cases on a spectrum with lymphoma)

#### Signs and Symptoms

- commonly presents over age 50, incidence rises with age; males > females
- dyspnea on exertion, nonproductive cough, constitutional symptoms, late inspiratory fine crackles at lung bases, clubbing

#### Investigations

- labs (nonspecific, autoimmune serology usually negative)
- CXR: reticular or reticulonodular pattern with lower lung predominance; may appreciate honeycombing in advanced disease
- high resolution CT: lower zone peripheral reticular markings, traction bronchiectasis, honeycombing, ground glass not prominent in IPF
- biopsy: rarely for UIP as honeycombing makes radiologic diagnosis possible

#### Treatment

- O<sub>2</sub>
- generally does not respond to immunosuppression
- N-acetylcysteine (anti-oxidant)
- lung transplantation for advanced disease
- mean survival of 3 to 5 yr after diagnosis

## SARCOIDOSIS

#### Definition

- idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
- characterized pathologically by non-caseating granulomas
- numerous HLA antigens have been shown to play a role and familial sarcoidosis is now recognized



#### IPF Prevalence

- Age 35-44: 2-7 per 100 000
- Age >75: 175 per 100 000



#### Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis

NEJM 2012;366:1968-1977

**Study:** Double blind, placebo-controlled, multicenter, RCT, 60-wk treatment period.

**Population:** 236 patients between 35 and 85 yr of age with IPF and mild-moderate lung function impairment (FVC >50%).

**Intervention:** Patients were randomized to receiving a combination of prednisone, azathioprine and NAC (combination therapy); NAC alone; or placebo.

**Outcome:** Change in longitudinal measurements of FVC over the treatment period.

**Results:** The combination therapy group was terminated early (mean follow-up of 32 wk) as patients in this group had an increased rate of death (8 vs. 1, P=0.01) and hospitalization (23 vs. 7, P<0.001) compared to placebo. Additionally, there was no evidence of physiological or clinical benefit for the combination therapy group.

**Conclusions:** Patients with IPF treated with combination therapy (NAC, azathioprine and prednisone) were at higher risk of death and hospitalization than the placebo group.

## Epidemiology

- typically affects young and middle-aged patients
- higher incidence among black Americans and people at northern latitudes e.g. Scandinavia, Canada

## Signs and Symptoms

- asymptomatic, cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
- chest exam often normal
- common extrapulmonary manifestations
  - cardiac (arrhythmias, sudden death)
  - eye involvement (anterior or posterior uveitis)
  - skin involvement (skin papules, erythema nodosum, lupus pernio)
  - peripheral lymphadenopathy
  - arthralgia
  - hepatomegaly ± splenomegaly
- less common extra-pulmonary manifestations involve bone, CNS and kidney
- two acute sarcoid syndromes
  - Löfgren's syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
  - Heerfordt-Waldenström syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy



Sarcoid is usually silent on auscultation.

## Investigations

- CBC (cytopenias from spleen or marrow involvement)
- serum electrolytes, creatinine, liver enzymes, calcium (hypercalcemia/hypercalciuria due to vitamin D activation by granulomas)
- hypergammaglobulinemia, occasionally RF positive
- elevated serum ACE (non-specific and non-sensitive)
- CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
- PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased DL<sub>CO</sub>
- ECG: to rule out conduction abnormalities
- slit-lamp eye exam: to rule out uveitis



Most common presentation: asymptomatic CXR finding



Hilar adenopathy refers to enlargement of mediastinal lymph nodes which is most often seen by standard CXR as spherical/ellipsoidal and/or calcified nodes.  
If unilateral think neoplasia, TB, or sarcoid.  
If bilateral think sarcoid or lymphoma.

## Diagnosis

- biopsy
  - transbronchial lung biopsy, transbronchial lymph node aspiration, endobronchial ultrasound guided surgical (EBUS) biopsy or mediastinoscopic lymph node biopsy for granulomas
  - in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

## Staging

- radiographic, based on CXR
  - Stage 0: normal radiograph
  - Stage I: bilateral hilar lymphadenopathy ± right paratracheal lymphadenopathy
  - Stage II: bilateral hilar lymphadenopathy and diffuse interstitial disease
  - Stage III: interstitial disease only (reticulonodular pattern or nodular pattern)
  - Stage IV: pulmonary fibrosis (honeycombing)

## Treatment

- 85% of stage I resolve spontaneously
- 50% of stage II resolve spontaneously
- steroids for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
- methotrexate or other immunosuppressives occasionally used

## Prognosis

- approximately 10% mortality secondary to progressive fibrosis of lung parenchyma



### Corticosteroids for Pulmonary Sarcoidosis

Cochrane DB Syst Rev 2005;CD001114

**Study:** Meta-analysis of 13 RCTs involving 1066 participants examining the use of steroids (oral or inhaled) in sarcoidosis.

**Results:** Oral steroids demonstrated an improvement in CXR (RR 1.46, 1.01 to 2.09). For inhaled corticosteroids, two studies showed no improvement in lung function and one study showed an improvement in diffusing capacity. No data on side-effects.

**Conclusions:** Oral steroids improve CXR findings and global scores of CXR, symptoms and spirometry over 3-24 mo, but do not improve lung function or modify disease course. Oral steroids may be of benefit for patients with Stage 2 and 3 disease.

## Known Etiologic Agents

### HYPERSENSITIVITY PNEUMONITIS

- also known as extrinsic allergic alveolitis
- non-IgE mediated inflammation of lung parenchyma (acute, subacute, and chronic forms)
- caused by sensitization to inhaled agents, usually organic dust
- pathology: airway-centered, poorly formed granulomas and lymphocytic inflammation
- exposure usually related to occupation or hobby
  - Farmer's Lung (*Thermophilic actinomycetes*)
  - Bird Breeder's/Bird Fancier's Lung (*Chlamydia psittaci* in bird droppings)
  - Humidifier Lung (*Aureobasidium pullulans*)
  - Sauna Taker's Lung (*Aureobasidium spp.*)

## Signs and Symptoms

- acute presentation: (4-6 h after exposure)
  - dyspnea, cough, fever, chills, malaise (lasting 18-24 h)
  - CXR: diffuse infiltrates
  - type III (immune complex) reaction
- subacute presentation: more insidious onset than acute presentation
- chronic presentation
  - insidious onset
  - dyspnea, cough, malaise, anorexia, weight loss
  - PFTs: progressively restrictive
  - CXR: predominantly upper lobe reticulonodular pattern
  - type IV (cell mediated, delayed hypersensitivity) reaction (see [Rheumatology](#), RH2)
- in both acute and chronic reactions, serum precipitins may be detectable (neither sensitive nor specific)



## Treatment

- early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
- systemic corticosteroids can relieve symptoms and speed resolution

## PNEUMOCONIOSES

- reaction to inhaled inorganic dusts 0.5-5  $\mu\text{m}$  in size
- no effective treatment, therefore key is exposure prevention through the use of protective equipment
- smoking cessation, annual influenza and pneumococcal vaccination, rehabilitation, lung transplant for endstage disease

**Table 18. Pneumoconioses**

Asbestosis	Silicosis	Coal Worker's Pneumoconiosis (CWP)
<ul style="list-style-type: none"> <li>• Exposure risks: insulation, shipyard, construction, brake linings, pipe fitters, plumbers</li> <li>• Slowly progressive diffuse interstitial fibrosis induced by inhaled asbestos fibres</li> <li>• Etiology: usually &gt; 10-20 yr of exposure; may develop with shorter but heavier exposure; typically prolonged interval (20-30 yr) between exposure and clinical disease</li> <li>• Signs and symptoms               <ul style="list-style-type: none"> <li>▪ Insidious onset</li> <li>▪ SOB</li> <li>▪ Cough: paroxysmal, non-productive</li> <li>▪ Fine end-respiratory crackles (increased at bases)</li> <li>▪ Clubbing (much more likely in asbestosis than silicosis or coal workers' pneumoconioses)</li> </ul> </li> <li>• Investigations: CXR               <ul style="list-style-type: none"> <li>▪ Lower &gt; upper lobe</li> <li>▪ Reticulonodular pattern, may develop IPF-like honeycombing</li> <li>▪ Asbestos exposure can also cause pleural and diaphragmatic plaques (<math>\pm</math> calcification), pleural effusion, round atelectasis</li> <li>▪ Microscopic examination reveals ferruginous bodies: yellow-brown rod-shaped structures which represent asbestos fibres coated in macrophages</li> </ul> </li> <li>• Complications: asbestos exposure increases risk of bronchogenic CA and malignant mesothelioma               <ul style="list-style-type: none"> <li>▪ Risk of lung cancer dramatically increased for smokers</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• At risk population: sandblasters, rock miners, stone cutters, quarry and highway workers</li> <li>• Etiology: generally requires &gt; 20 yr exposure; may develop with much shorter but heavier exposure</li> <li>• Signs and symptoms: dyspnea, cough and wheezing</li> <li>• Investigations: CXR               <ul style="list-style-type: none"> <li>▪ Upper &gt; lower lobe</li> <li>▪ Early: nodular disease (simple pneumoconiosis), lung function usually normal</li> <li>▪ Late: nodules coalesce into masses (progressive massive fibrosis)</li> </ul> </li> <li>• Possible hilar lymph node enlargement (frequently calcified), especially "egg shell" calcification</li> <li>• Complications: mycobacterial infection (e.g. TB)</li> </ul>	<ul style="list-style-type: none"> <li>• At risk population: coal workers, graphite workers</li> <li>• Etiology: coal and silica, coal is less fibrogenic than silica</li> <li>• Pathologic hallmark is coal macule</li> <li>• Simple CWP               <ul style="list-style-type: none"> <li>▪ No signs or symptoms, usually normal lung function</li> <li>▪ CXR: multiple nodular opacities, mostly upper lobe</li> </ul> </li> <li>• Complicated CWP (also known as progressive massive fibrosis)               <ul style="list-style-type: none"> <li>▪ Dyspnea</li> <li>▪ CXR: opacities larger and coalesce</li> </ul> </li> <li>• Course: few patients progress to complicated CWP</li> <li>• Caplan's syndrome: rheumatoid arthritis and CWP present as larger nodules</li> </ul>



Diaphragmatic plaques are highly suggestive of asbestosis, especially if bilateral.



### CXR Fibrotic Patterns

- Asbestosis: lower > upper lobes
- Silicosis: upper > lower lobes
- Coal: upper > lower lobes



Remember to involve occupational health at place of work for data collection and treatment plan. Also counsel re: worker's insurance as per jurisdiction (e.g. Workers Safety Insurance Board (WSIB) in Ontario).

## ILD ASSOCIATED WITH DRUGS OR TREATMENTS

### Drug-Induced

- antineoplastic agents: bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate, chlorambucil, BCNU (carmustine)
- antibiotics: nitrofurantoin, penicillin, sulfonamide
- cardiovascular drugs: amiodarone, tocainide
- anti-inflammatory agents: methotrexate, penicillamine
- gold salts
- illicit drugs (heroin, methadone)
- rituximab, anti-TNF  $\alpha$  agents (infliximab, etanercept, adalimumab)

### Radiation-Induced

- early pneumonitis: approximately 6 wk post-exposure
- late fibrosis: 6-12 mo post-exposure
- infiltrates conform to the shape of the radiation field

# Pulmonary Vascular Disease



## Pulmonary Hypertension

### Definition

- mean pulmonary arterial pressure >25 mmHg at rest and >30 mmHg with exercise, or a systolic pulmonary artery pressure of >40 mmHg at rest
- in the past, pulmonary HTN was classified as primary or secondary pulmonary HTN, but this classification was modified to a more clinically useful, treatment based classification (Table 19)

**Table 19. World Health Organization Classification of Pulmonary Hypertension**

Classification	Some Causes	Treatment Options	Consider in All Patient's with PH
<b>I. Pulmonary arterial HTN</b>	Idiopathic Collagen vascular disease (scleroderma, SLE, RA) Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome) Portopulmonary HTN HIV infection Drugs and toxins (e.g. anorexigens) Pulmonary veno-occlusive disease Schistosomiasis Pulmonary capillary hemangiomatosis Sickle cell disease	No effective treatment CCB's or advanced therapy often needed The latter includes: prostanoids, endothelin receptor antagonists, PDE5 inhibitors Lung transplantation	Oxygen therapy Exercise Consider anticoagulation
<b>II. Pulmonary HTN due to the left heart disease</b>	Left-sided atrial or ventricular heart disease (e.g. LV dysfunction) Left-sided valvular heart disease (e.g. aortic stenosis, mitral stenosis)	Treat underlying heart disease	
<b>III. Pulmonary HTN due to lung disease and/or hypoxia</b>	Parenchymal lung disease (COPD, interstitial fibrosis, cystic fibrosis) Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep disordered breathing)	Treat underlying cause of hypoxia and correct with supplemental oxygen (proven mortality benefit)	
<b>IV. Chronic thromboembolic pulmonary HTN (CTEPH)</b>	Thromboembolic obstruction of proximal pulmonary arteries Obstruction of distal pulmonary arteries – PE (thrombus, foreign material, tumour, in situ thrombosis)	Anticoagulation, thromboendarterectomy	
<b>V. Pulmonary HTN with unclear multifactorial mechanisms</b>	Hematologic disorders Systemic disorders (e.g. sarcoidosis) Metabolic disorders Extrinsic compression of central pulmonary veins (tumour, adenopathy, fibrosing mediastinitis)	Treat underlying cause	

Adapted from Simonneau, et al. J Am Coll of Cardiol 2009

### Mechanisms of Pulmonary Hypertension (simplified)

- hypoxic vasoconstriction
  - chronic hypoxia causes pulmonary vasoconstriction by a variety of actions on the pulmonary artery endothelium and smooth muscle cells, such as: down regulation of endothelial nitric oxide synthase and alteration of voltage gated potassium channels leading to vasoconstriction
  - causes: COPD, chronic alveolar hypoxia
- decreased area of pulmonary vascular bed
  - leads to a rise in resting pulmonary arterial pressure
  - causes: collagen vascular disease, HIV infection, drugs and toxins, thrombotic or embolic disease, inflammatory, pulmonary capillary hemangiomatosis, interstitial fibrosis, CF
- volume and pressure overload
  - significant HTN only occurs with excessive volume overload, since pulmonary artery pressure will not rise in otherwise normal lung until pulmonary blood flow exceeds 2.5x the basal rate
  - causes: congenital systemic to pulmonary shunts (e.g. VSD, ASD, PDA), portopulmonary HTN, left-sided heart conditions, pulmonary veno-occlusive disease, extrinsic compression of central pulmonary veins

## IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (aka PRIMARY PULMONARY HYPERTENSION)

### Definition

- pulmonary HTN in the absence of a demonstrable cause
- exclude:
  - left-sided cardiac valvular disease
  - myocardial disease
  - congenital heart disease
  - any clinically significant parenchymal lung disease
  - systemic connective-tissue disease
  - chronic thromboembolic disease

### Epidemiology

- usually presents in young women (20-40 yr); mean age of diagnosis is 36 yr
- most cases are sporadic; familial predisposition in 10% of cases, some linked to mutations in BMPR2
- may be associated with the use of anorexic drugs (e.g. Aminorex®, Fenfluramine®), also amphetamines and cocaine

### Signs and Symptoms

- exertional dyspnea, fatigue, syncope, exertional chest pain, Raynaud's phenomenon
- see Table 20

**Table 20. Signs and Symptoms of Pulmonary Hypertension**

Symptoms	Signs
Dyspnea	Loud, palpable P <sub>2</sub>
Fatigue	RV heave
Substernal chest pain	Right-sided S <sub>4</sub> (due to RVH)
Syncope	Systolic murmur [tricuspid regurgitation (TR)]
Symptoms of underlying disease	If RV failure: right sided S <sub>3</sub> , increased JVP, positive HJR, peripheral edema, TR

### Investigations

- CXR: enlarged central pulmonary arteries, cardiac changes due to RV enlargement (filling of retrosternal air space)
- ECG
  - RVH/right-sided strain (see [Cardiology and Cardiovascular Surgery](#), C7)
- 2-D echo doppler assessment of right ventricular systolic pressure
- cardiac catheterization: direct measurement of pulmonary artery pressures (necessary to confirm diagnosis)
- PFTs to assess for underlying lung disease: DL<sub>CO</sub> usually reduced
- CT angiogram to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary HTN. Other serologic markers can be used in the appropriate clinical setting

### Treatment

- see Table 19

### Prognosis

- 2-3 yr mean survival from time of diagnosis
- survival decreases to approximately 1 yr if severe pulmonary HTN or right-heart failure



Pulmonary arterial pressures are measured by pulmonary artery catheters (aka Swan-Ganz catheter) which are inserted into a large vein (often internal jugular). A balloon at the end of the catheter tip is inflated causing the catheter to advance through the right side of the heart and into the pulmonary artery. This allows for the measurement of RA, RV, PA and pulmonary capillary wedge pressures as well as sampling of mixed venous blood. A thermistor near the end of the catheter also allows for assessment of cardiac output by thermodilution.



### Guidelines for Vasodilator Response in Pulmonary Arterial HTN

- Patients with IPAH that respond to vasodilators acutely, have an improved survival with long-term use of CCBs
- Vasoreactivity testing: short-acting agent such as IV epoprostenol, IV adenosine or inhaled NO
- Positive vasodilator response: mean PAP fall of at least 10 mmHg to ≤40 mmHg with an increased or unchanged cardiac output (European Society of Cardiology)
- Positive vasodilator response: should be considered as candidate for trial of oral CCB therapy

Medical Therapy for Pulmonary Arterial Hypertension. ACCP Evidence-Based Clinical Practice Guidelines. *Chest* 2004;(Suppl)06:126



## Pulmonary Embolism (PE)

### Definition

- lodging of a blood clot in the pulmonary arterial tree with subsequent increase in pulmonary vascular resistance, impaired V/Q matching, and possibly reduced pulmonary blood flow

### Etiology and Pathophysiology

- one of the most common causes of preventable death in the hospital
- proximal leg thrombi (popliteal, femoral or iliac veins) are the source of most clinically recognized pulmonary emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE
- fewer than 30% of patients have clinical evidence of DVT (e.g. leg swelling, pain or tenderness)
- always suspect PE if patient develops fever, sudden dyspnea, chest pain, or collapse 1-2 wk after surgery



### Virchow's Triad

- Venous stasis
- Endothelial cell damage
- Hypercoagulable states



## Risk Factors

- stasis
  - immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
  - obesity, CHF
  - chronic venous insufficiency
- endothelial cell damage
  - post-operative injury, trauma
- hypercoagulable states
  - underlying malignancy (particularly adenocarcinoma)
  - cancer treatment (chemotherapy, hormonal)
  - exogenous estrogen administration (OCP, HRT)
  - pregnancy, post-partum
  - prior history of DVT/PE, family history
  - nephrotic syndrome
  - coagulopathies: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease
- increasing age

## Investigations (if highly suspicious, go straight to spiral CT angiogram)

- see [Emergency Medicine](#), Figure 12, ER34
- **Pulmonary Angiogram (Gold Standard)**
  - filling defect indicative of embolus; negative angiogram excludes clinically relevant PE
  - more invasive, and harder to perform than CT, therefore done infrequently
- D-dimer (products of thrombotic/fibrinolytic process)
  - highly sensitive D-dimer result can exclude DVT/PE if pretest probability is already low
  - little value if pretest probability is high
  - if D-dimer positive, will need further evaluation with compression U/S
- CT angiogram is both sensitive and specific for PE
  - diagnosis and management uncertain for small filling defects
  - spiral CT may identify an alternative diagnosis if PE is not present
  - CT scanning of the proximal leg and pelvic veins can be done at the same time and may be helpful
- venous duplex U/S or Doppler
  - with leg symptoms
    - ♦ positive test rules in proximal DVT
    - ♦ negative test rules out proximal DVT
  - without leg symptoms
    - ♦ positive test rules in proximal DVT
    - ♦ negative test does not rule out a DVT: patient may have non-occlusive or calf DVT
- ECG
  - findings not sensitive or specific
  - sinus tachycardia most common; may see non-specific ST segment and T wave changes
  - RV strain, RAD, RBBB, S1-Q3-T3 with massive embolization
- CXR
  - frequently normal; no specific features
  - atelectasis (subsegmental), elevation of a hemidiaphragm
  - pleural effusion: usually small
  - Hampton's hump: cone-shaped area of peripheral opacification representing infarction
  - Westermark's sign: dilated proximal pulmonary artery with distal oligemia/decreased vascular markings (difficult to assess without prior films)
  - dilatation of proximal PA: rare
- V/Q scan (very sensitive but low specificity)
  - order scan if
    - ♦ CXR normal, no COPD
    - ♦ contraindication to CT (contrast allergy, renal dysfunction, pregnancy)
  - avoid V/Q scan if
    - ♦ CXR abnormal or COPD
    - ♦ inpatient
    - ♦ suspect massive PE
  - results
    - ♦ normal: excludes the diagnosis of PE
    - ♦ high probability: most likely means PE present, unless pre-test probability is low
    - ♦ 60% of V/Q scans are nondiagnostic
- echocardiogram
  - useful to assess massive or chronic PE
  - not routinely done
- ABG
  - no diagnostic use in PE (insensitive and nonspecific)
  - may show respiratory alkalosis (due to hyperventilation)



### Clinical Prediction Rule for Pulmonary Embolism

*J Thromb Hemost* 2000;83:416-420

Wells Criteria

Risk Factors	Points
Clinical signs of DVT	3.0
No more likely alternative diagnosis (using H&P, CXR, ECG)	3.0
Immobilization or surgery in the previous 4 wk	1.5
Previous PE/DVT	1.5
HR >100 beats/min	1.5
Hemoptysis	1.0
Malignancy	1.0

### Clinical probability

Low (0-2)	3%
Intermediate (3-6)	28%
High (>6)	78%

Modified Wells: >4 PE likely; ≤4 PE unlikely

*JAMA* 2006



### PE Rule-out Criteria (PERC)

#### Prospective Multicenter Evaluation of the Pulmonary Embolism Rule-out Criteria

*J Thromb Hemost* 2008;6:772

- Age less than 50 yr
- Heart rate less than 100 bpm
- Oxyhemoglobin saturation ≥95 percent
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery or trauma requiring hospitalization within the past 4 wk

Acute PE can probably be excluded without further diagnostic testing if the patient meets all PERC criteria AND there is a low clinical suspicion for PE, according to either the Wells criteria or a low gestalt probability determined by the clinician prior to diagnostic testing for PE.



### Evaluation of a Suspected Pulmonary Embolism

*Low clinical probability of embolism:*

**D-dimer (+ve) → CT scan (+ve) → ruled in**  
(-ve) ruled out (-ve) ruled out

*Intermediate or high probability:*

**CT scan (-ve) → ruled out**  
(+ve) ruled in

*Notes:*

- Use D-dimers only if low clinical probability, otherwise, go straight to spiral CT
- If using V/Q scans (CT contrast allergy or renal failure):
  - Negative V/Q scan rules out the diagnosis
  - High probability V/Q scan only rules in the diagnosis if have high clinical suspicion
  - Inconclusive V/Q scan requires leg U/S to look for DVT or spiral CT



Classic ECG finding of PE is S<sub>1</sub>-Q<sub>3</sub>-T<sub>3</sub> (inverted T<sub>3</sub>), but most commonly see only sinus tachycardia.



D-dimer is elevated in patients with recent surgery, cancer, inflammation, infection, and severe renal dysfunction. It has good sensitivity and negative predictive value, but poor specificity and positive predictive value.

## Treatment

- admit for observation (patients with DVT only are often sent home on LMWH)
- oxygen: supplemental O<sub>2</sub> if hypoxemic or short of breath
- pain relief: analgesics if chest pain – narcotics or acetaminophen
- acute anticoagulation: therapeutic-dose SC LMWH or IV heparin – start ASAP
  - anticoagulation stops clot propagation, prevents new clots and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months
  - get baseline CBC, INR, aPTT ± renal function ± liver function
  - for SC LMWH: dalteparin 200 U/kg once daily or enoxaparin 1 mg/kg bid – no lab monitoring – avoid or reduce dose in renal dysfunction
  - for IV heparin: bolus of 75 U/kg (usually 5,000 U) followed by infusion starting at 20 U/kg/h – aim for aPTT 2-3x control
- long term anticoagulation
  - warfarin: start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 d and until INR in target range of 2-3 for at least 2 d
  - LMWH instead of warfarin for pregnancy, active cancer, or high bleeding risk patients
  - dabigatran has been shown to have lower bleeding risk than warfarin
- IV thrombolytic therapy
  - if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
  - hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding
- interventional thrombolytic therapy
  - massive PE is preferentially treated with catheter-directed thrombolysis by an interventional radiologist
  - works better than IV thrombolytic therapy and fewer contraindications
- IVC filter: only if recent proximal DVT + absolute contraindication to anticoagulation
- duration of long-term anticoagulation: individualized, however generally:
  - if reversible cause for PE (surgery, injury, pregnancy, etc.): 3-6 mo
  - if PE unprovoked: 6 mo to indefinite
  - if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite

## Thromboprophylaxis

- mandatory for most hospital patients: reduces DVT, PE, all-cause mortality, cost-effective
- start ASAP
- continue at least until discharge or recommend extending for 35 d postoperatively, if major orthopedic surgery

**Table 21. VTE Risk Categories and Prophylaxis** (see [Hematology](#), H32)

Risk Group	Prophylaxis Options
<b>Low thrombosis risk:</b> Medical patients: fully mobile Surgery: <30 min, fully mobile	No specific prophylaxis Frequent ambulation
<b>Moderate thrombosis risk:</b> Most general, gynecologic, urologic surgery Sick medical patients	LMWH Low dose unfractionated heparin Fondaparinux
<b>High thrombosis risk:</b> Arthroplasty, hip fracture surgery Major trauma, spinal cord injury	LMWH Fondaparinux Warfarin (INR 2-3) Dabigatran Apixaban Rivaroxaban Low dose unfractionated heparin
<b>High bleeding risk:</b> Neurosurgery, intracranial bleed Active bleeding	TED stockings, pneumatic compression devices LMWH or low dose heparin when bleeding risk decreases



### Workup for Idiopathic VTE

**Thrombophilia Workup:** recurrent or idiopathic DVT/PE; age <50, FHx, unusual location, massive.

**Malignancy Workup:** 12% of patients with idiopathic VTE will have a malignancy.



### Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism

*NEJM* 2013;368:709-718

**Study:** Two double blind, RCTs; one comparing against placebo, the other against active treatment. **Population:** 4199 patients (2856 in active-control study, 1343 in placebo-control study) with VTE who had completed at least 3 mo of therapy.

**Intervention:** In the active-control study, patients randomized to either 150 mg dabigatran or warfarin (INR 2.0-3.0). Patients in the placebo-control study received either 150 mg dabigatran or placebo.

**Outcome:** Recurrence of VTE, risk of major or clinically relevant bleed.

**Results:** In the active-control study, there was a hazard ratio (HR) of 1.44 (95% CI 0.78-2.64 for non-inferiority) of recurrent VTE with dabigatran vs. warfarin. HR of major or clinically relevant bleed was 0.54 (95% CI 0.41-0.71). In the placebo-control study, the HR of VTE with dabigatran vs. placebo was 0.08 (95% CI 0.02-0.25). HR of major or clinically relevant bleed was 2.92 (95% CI 1.52-5.60).

**Conclusions:** Dabigatran appears to be non-inferior to warfarin in the prevention of VTE recurrence. Dabigatran is associated with a lower risk of major or clinically relevant bleed than warfarin, but greater than placebo.



### Excluding Pulmonary Embolism at Bedside without Diagnostic Imaging

*Ann Intern Med* 2001;135:98-107

**Study:** Multicentre, prospective cohort study.

**Patients:** 930 patients with suspected PE at emergency departments at 4 tertiary care hospitals in Canada.

**Intervention:** A Wells score was used to determine patient's pretest probability (PTP) of PE along with a D-dimer test was performed. Patients with low PTP and a negative D-dimer test had no further testing and the diagnosis of PE was excluded. All other patients had V/Q scanning, and if non-diagnostic, had bilateral deep venous ultrasonography. Further serial ultrasonography and angiography were done depending on the patients PTP and lung-scanning results.


**Main outcomes:** Diagnosis of PE and the development of thromboembolic events at 3 mo follow-up.

**Results:** One of 759 patients in whom PE was initially ruled out developed a thromboembolic event during follow-up (0.1% [CI 0.0%-0.7%]). One of the 437 patients with negative D-dimers and low clinical PTP developed PE during follow up (NPV 99.5%, CI 99.1-100%).

**Conclusion:** Managing patients with suspected pulmonary embolism on the basis of PTP and D-dimer results is safe and decreases the need for diagnostic imaging.

## Pulmonary Vasculitis

Table 22. Pulmonary Vasculitis

Disease	Definition	Pulmonary Features	Extra-pulmonary Features	Investigations	Treatment
<b>Granulomatosis with Polyangiitis (Wegener's Granulomatosis)</b> (see <a href="#">Nephrology</a> , NP24)	Systemic vasculitis of medium and small arteries	Necrotizing granulomatous lesions of the upper and lower respiratory tract	Focal necrotizing lesions of arteries and veins; Crescentic glomerulonephritis	CXR: nodules, cavities, and alveolar opacities c-ANCA Tissue confirmation	Corticosteroids and cyclophosphamide or rituximab
<b>Churg-Strauss Syndrome (Allergic Granulomatosis and Angiitis)</b>	Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia	Asthma Infiltrates	Life-threatening systemic vasculitis involving the lungs, pericardium and heart, kidneys, skin, and PNS (mononeuritis multiplex)	Peripheral eosinophilia is the most common finding p-ANCA may be positive Biopsy involved tissue	Corticosteroids
<b>Goodpasture's Disease</b> (see <a href="#">Nephrology</a> , NP24)	A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung	Hemoptysis May follow an influenza infection	Anemia	CXR: may see alveolar infiltrates if hemorrhage is profuse ELISA test with anti-GBM antibodies Renal biopsy/indirect immunofluorescence shows linear staining	Acutely: corticosteroids, plasmapheresis Immunosuppressive therapy Severe cases: bilateral nephrectomy
 <b>Systemic Lupus Erythematosus, Rheumatoid Arthritis, Scleroderma</b>	See <a href="#">Rheumatology</a> , RH8				

## Pulmonary Edema

- see [Cardiology and Cardiovascular Surgery](#), C32



Scleroderma is the most common collagen vascular disease affecting the lung.

## Diseases of the Mediastinum and Pleura

### Mediastinal Masses

#### Definition

- mediastinum: bound by the thoracic inlet, diaphragm, sternum, vertebral bodies and the pleura
- can be broken down into 3 compartments: anterior, middle and posterior (see sidebar)

#### Etiology and Pathophysiology

- diagnosis is made by location and patient's age
- anterior compartment: more likely to be malignant
  - "Five Ts" (see sidebar), lymphoma, lipoma, pericardial cyst
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumour, lymphoma, lymph node enlargement, aortic aneurysm
- posterior compartment
  - neurogenic tumours, meningocele, enteric cysts, lymphoma, diaphragmatic hernias, esophageal tumour, aortic aneurysm

#### Signs and Symptoms

- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner's syndrome, facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes [e.g. myasthenia gravis (thymomas)]

#### Investigations

- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumours
- U/S (best for assessment of structures in close proximity to the heart and pericardium)
- radionuclide scanning:  $^{131}\text{I}$  (for thyroid), gallium (for lymphoma)
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP,  $\beta$ -hCG
- biopsy (mediastinoscopy, percutaneous needle aspiration)



#### Anterior Compartment

##### 5 Ts

Thymoma  
Thyroid enlargement (goiter)  
Teratoma  
Thoracic aortic aneurysm  
Tumours  
(lymphoma, parathyroid, esophageal, angiomatous)



#### Mediastinal Components

**Anterior:** sternum to posterior aspect of heart and great vessels. Includes: thymus, extrapericardial aorta and branches, great veins, lymphatic tissues.  
**Middle:** pericardium (anteriorly) posterior pericardial reflection, diaphragm, thoracic inlet. Includes: heart, intrapericardial great vessels, pericardium, trachea.  
**Posterior:** posterior pericardial reflection, posterior border of vertebral bodies, first rib to the diaphragm. Includes: esophagus, vagus nerve, thoracic duct, sympathetic chain, azygous venous system.



#### Horner's Syndrome

Ptosis, Miosis, Anhidrosis

## Management

- excision if symptomatic enlarging benign masses or concerns of malignancy
- resect bronchogenic cysts and localized neurogenic tumours via minimally invasive video assisted procedures
- exploration via sternotomy or thoracotomy
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
- $\pm$  post-op radiotherapy/chemotherapy if malignant

## Mediastinitis

- commonest causes: postoperative complications of cardiovascular or thoracic surgical procedures

### Acute

- etiology
  - complication of endoscopy (e.g. esophageal perforation providing entry point for infection)
  - esophageal or cardiac surgery
  - tumour necrosis
- signs and symptoms
  - fever, substernal pain
  - pneumomediastinum, mediastinal compression
  - Hamman's sign (auscultatory "crunch" during cardiac systole)
- treatment
  - antibiotics, drainage,  $\pm$  surgical closure of perforation

### Chronic

- usually granulomatous process or fibrosis related to previous infection (e.g. histoplasmosis, TB, sarcoidosis, syphilis)



#### Multidetector Computed Tomography for Acute Pulmonary Embolism (PIOPED II Trial)

NEJM 2006;354:2317-2327

**Study:** Multicentre, prospective study investigating accuracy of computed tomography angiography (CTA) alone and combined with venous phase imaging (CTA-CTV) for the diagnosis of PE.

**Patients:** 824 patients of several thousand eligible for study received reference diagnosis to confirm absence or presence of PE (V/Q scan, venous compression U/S of lower extremities, and pulmonary digital-subtraction angiography (DSA) if necessary). To confirm absence, patients in whom PE was excluded were telephoned 3-6 mo after enrollment. Any deaths were reviewed by an outcome committee. All patients enrolled also underwent clinical assessment of PE (including a Wells score) prior to imaging.

**Outcomes:** Diagnosis of pulmonary embolism.

**Results:** 773 of 824 patients had adequate CTAs for interpretation. PE was diagnosed in 192 of the 824 patients. Sensitivity was 83% (150 of 181 patients, 95% CI, 0.76-0.92) and specificity was 96% (567 of 592 patients, 95% CI, 0.93-0.97). However, the predictive value of CTA-CTV varied when clinical pre-test probability was taken into account. PPV of CTA for high, intermediate and low clinical probability were 96% (95% CI, 0.78-0.99), 92% (95% CI, 0.84-0.96), and 58% (95% CI, 0.40-0.73) respectively. NPV of CTA for high, intermediate and low clinical probability were 60% (95% CI, 0.32-0.83), 89% (95% CI, 0.82-0.93), and 96% (95% CI, 0.92-0.98) respectively.

**Conclusion:** CTA is effective for diagnosing or excluding PE in accordance with assessment of clinical pretest probability. When clinical probability is inconsistent with imaging results, further investigations are required to rule out PE.



## Pleural Effusions

### Definition

- excess amount of fluid in the pleural space (normally up to 25 mL)

### Etiology

- disruption of normal equilibrium between pleural fluid formation/entry and pleural fluid absorption/exit
- pleural effusions are classified as transudative or exudative
  - distinguish clinically using Light's Criteria (Table 23), which has a sensitivity of 98% and specificity of 83% for identifying exudative pleural effusions

**Table 23. Laboratory Values in Transudative and Exudative Pleural Effusion ("Light's Criteria and Modified Light's Criteria")**

	Light's Criteria	Modified Light's Criteria
Protein – pleural/serum	>0.5	>0.5
LDH – pleural/serum	>0.6	>0.6
Pleural LDH	>2/3 upper limit of N serum LDH	>0.45 upper limit of N serum LDH
Exudate = at least one criteria met		

Ann Intern Med 1979;77:507-513  
Chest 1997;111:970-980

### Transudative Pleural Effusions

- pathophysiology: alteration of systemic factors that affect the formation and absorption of pleural fluid (e.g. increased capillary hydrostatic pressure, decreased plasma oncotic pressure)
- etiology
  - CHF: usually right-sided or bilateral cirrhosis
  - nephrotic syndrome, protein losing enteropathy, cirrhosis
  - pulmonary embolism (may cause transudative but more often causes exudative effusion)
  - peritoneal dialysis, hypothyroidism, CF, urinothorax

### Exudative Pleural Effusions

- pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction
- etiology (see Table 24)



**Transudative** effusions are usually bilateral, not unilateral.

**Exudative** effusions can be bilateral or unilateral.



All criteria for transudate must be fulfilled to be considered a transudative effusion. If any one of the criteria for exudates is met – it is an exudate.

**Table 24. Exudative Pleural Effusion Etiologies**

Etiology	Examples
<b>Infectious</b>	Parapneumonic effusion (associated with bacterial pneumonia, lung abscess) Empyema (bacterial, fungal, TB) TB pleuritis Viral infection
<b>Malignancy</b>	Lung carcinoma (35%) Lymphoma (10%) Metastases: breast (25%), ovary, kidney Mesothelioma
<b>Inflammatory</b>	Collagen vascular diseases: RA, SLE Pulmonary embolism Post-CABG Drug reaction
<b>Intra-abdominal</b>	Subphrenic abscess Pancreatic disease (elevated pleural fluid amylase) Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)
<b>Intra-thoracic</b>	Esophageal perforation (elevated fluid amylase)
<b>Trauma</b>	Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space, due to trauma, tumour Hemothorax: rupture of a blood vessel, commonly by trauma or tumours Pneumothorax (spontaneous, traumatic, tension)

### Signs and Symptoms

- often asymptomatic
- dyspnea: varies with size of effusion and underlying lung function
- pleuritic chest pain
- inspection: trachea deviates away from effusion, ipsilateral decreased expansion
- percussion: decreased tactile fremitus, dullness
- auscultation: decreased breath sounds, bronchial breathing and egophony at upper level, pleural friction rub

### Investigations

- CXR
  - must have >200 mL of pleural fluid for visualization on PA film
  - lateral: >50 mL leads to blunting of posterior costophrenic angle
  - PA: blunting of lateral costophrenic angle
  - dense opacification of lung fields with concave meniscus
  - decubitus: fluid will shift unless it is loculated
  - supine: fluid will appear as general haziness
- thoracentesis: indicated if pleural effusion is a new finding; be sure to send off blood work (LDH, glucose, protein) at the same time for comparison
  - risk of re-expansion pulmonary edema if >1.5 L of fluid is removed
  - inspect for colour, character, and odour of fluid
  - analyze fluid (see Tables 23 and 25)
- pleural biopsy: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology negative)
- ± U/S: detects small effusions and can guide thoracentesis
- treatment depends on cause, ± drainage if symptomatic
- CT can be helpful in differentiating parenchymal from pleural abnormalities

**Table 25. Analysis of Pleural Effusion**

Measure	Purpose
Protein, LDH	Transudate vs. exudate (see Table 23)
Gram stain, Ziehl-Nielsen stain (TB), culture	Looking for specific organisms
Cell count differential	Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, serositis)
Cytology	Malignancy, infection
Glucose (low)	RA, TB, empyema, malignancy, esophageal rupture
Rheumatoid factor, ANA, complement	Collagen vascular disease
Amylase	Pancreatitis, esophageal perforation, malignancy
pH	Empyema <7.2, TB and mesothelioma <7.3
Blood	Mostly traumatic, malignancy, PE with infarction, TB
Triglycerides	Chylothorax from thoracic duct leakage, mostly due to trauma, lung CA, or lymphoma



#### Appearance of Pleural Fluid

- Bloody: trauma, malignancy
- White: chylothorax, empyema
- Black: aspergillosis, amoebic liver abscess
- Yellow-green: rheumatoid pleurisy
- Viscous: malignant mesothelioma
- Ammonia odour: urinothorax
- Food particles: esophageal rupture



#### Role of CT in Pleural Effusion

- To assess for fluid loculation, pleural thickening and nodules, parenchymal abnormalities and adenopathy
- Helps to distinguish benign from malignant effusion and transudative from exudative effusion
- May not distinguish empyema from parapneumonic effusion

#### Features of Malignant Effusion

- Multiple pleural nodules
- Nodular pleural thickening

#### Features of Exudative Effusion

- Loculation
- Pleural thickening
- Pleural nodules
- Extrapleural fat of increased density



**Treatment**

- thoracentesis
- treat underlying cause
- consider indwelling pleural catheter or pleurodesis in refractory effusions

**Complicated Parapneumonic Effusion**

- persistent bacteria in the pleural space, but fluid is non-purulent
- neutrophils, pleural fluid acidosis (pH <7.00), and high LDH
- often no bacteria grown, since rapidly cleared from pleural space
- fibrin layer leading to loculation of pleural fluid
- treatment: antibiotics and drainage, treat as an empyema

**Empyema****Definition**

- pus in pleural space or an effusion with organisms seen on a Gram stain or culture (i.e. pleural fluid is grossly purulent)
- positive culture is not required for diagnosis

**Etiology**

- contiguous spread from lung infection (most commonly anaerobes), or infection through chest wall (e.g. trauma, surgery)

**Signs and Symptoms**

- fever, pleuritic chest pain

**Investigations**

- CT chest
- thoracentesis
- PMNs (lymphocytes in TB) ± visible organisms on Gram stain

**Treatment**

- antibiotic therapy for at least 4-6 wk (rarely effective alone)
- complete pleural drainage with chest tube
- if loculated, more difficult to drain – may require surgical drainage video-assisted thorascopic surgery (VATS)

**Atelectasis**

- see [General Surgery](#), GS10

**Pneumothorax****Definition**

- presence of air in the pleural space

**Pathophysiology**

- increased intrapleural pressure reduces lung inflation

**Etiology**

- traumatic: penetrating or non-penetrating chest injuries
- iatrogenic (central venous catheter, thoracentesis, mechanical ventilation with barotrauma)
- spontaneous (no history of trauma)
  - primary (no underlying lung disease)
    - ♦ spontaneous rupture of apical subpleural bleb of lung into pleural space
    - ♦ predominantly tall, healthy, young males
  - secondary (underlying lung disease)
    - ♦ rupture of subpleural bleb which migrates along bronchioalveolar sheath to the mediastinum then to the intrapleural space
    - ♦ necrosis of lung tissue adjacent to pleural surface (e.g. pneumonia, abscess, PCP, lung CA, emphysema)

**Signs and Symptoms**

- can be asymptomatic
- acute-onset pleuritic chest pain, dyspnea
- tachypnea, tachycardia

**Pleural Effusions****Simple Effusion**

pH >7.2, LDH <1/2 serum, glucose >2.2

**Complicated Effusion**

pH <7.2, LDH >1/2 serum, glucose <2.2, positive Gram stain  
Needs drainage



When possible, organism-directed therapy, guided by culture sensitivities or local patterns of drug resistance, should be utilized.

**Need to Rule Out Life-Threatening Tension Pneumothorax**

If pneumothorax with:

- Severe respiratory distress
- Tracheal deviation to contralateral side
- Distended neck veins (↑ JVP)
- Hypotension

**Do not perform CXR.**

**Needs immediate treatment.**

See [Emergency Medicine](#), ER11



- tracheal deviation (contralateral deviation in tension pneumothorax)
- ipsilateral diminished chest expansion
- decreased tactile/vocal fremitus
- hyperresonance
- ipsilateral diminished breath sounds

### Investigations

- CXR
  - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  - large: increased density and decreased volume of lung on side of pneumothorax
  - see [Medical Imaging](#), MI8



### Treatment

- small pneumothoraces (<20% with no signs of respiratory/circulatory collapse) resolve spontaneously; breathing 100% oxygen accelerates resorption of air
- small intercostal tube with Heimlich valve for most spontaneous pneumothoraces
- large pneumothoraces or those complicating underlying lung disease require placement of a chest tube connected to underwater seal  $\pm$  suction
- for repeated episodes: pleurodesis with sclerosing agent or apical bullectomy and abrasion
- treat underlying cause (e.g. antibiotic for PCP)

## Asbestos-Related Pleural Disease and Mesothelioma

### Etiology and Pathophysiology

- benign manifestations of asbestos exposure
  - “benign asbestos pleural effusion”
    - ♦ exudative effusion, typically  $\approx$ 10 yr after exposure, resolves
  - pleural plaques, usually calcified
    - ♦ marker of exposure; usually an asymptomatic radiologic finding
- mesothelioma
  - primary malignancy of the pleura
  - decades after asbestos exposure (even with limited exposure)
  - smoking not a risk factor, but asbestos and smoking synergistically increase risk of lung cancer

### Signs and Symptoms

- persistent chest pain, dyspnea, cough, bloody pleural effusion, weight loss

### Investigations

- biopsy (pleuroscopic or open)
- needle biopsy may seed needle tract with tumour

### Treatment

- resection (extrapleural pneumonectomy) requires careful patient selection; rarely successful (average survival <1 yr)

## Respiratory Failure



### Definition

- failure of respiratory system to maintain normal blood gases
- hypoxemic ( $P_aO_2 < 60$  mmHg)
- hypercapnic ( $P_aCO_2 > 50$  mmHg)
- acute vs. chronic (compensatory mechanisms activated)

### Signs and Symptoms

- signs of underlying disease
- hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale
- hypercapnia: headache, dyspnea, drowsiness, asterixis, warm periphery, plethora, increased ICP (secondary to vasodilatation)

### Investigations

- serial ABGs
- CXR and/or CT, bronchoscopy to characterize underlying cause if unclear

## Hypoxemic Respiratory Failure

### Definition

- $P_aO_2$  decreased,  $P_aCO_2$  normal or decreased

### Treatment

- reverse the underlying pathology
- oxygen therapy: maintain oxygenation (if shunt present, supplemental  $O_2$  is less effective; see [Anesthesia](#), A10, for oxygen delivery systems)
- ventilation, BiPAP and PEEP/CPAP (see *Mechanical Ventilation*, R26): positive pressure can recruit alveoli and redistribute lung fluid
- improve cardiac output:  $\pm$  hemodynamic support (fluids, vasopressors, inotropes), reduction of  $O_2$  requirements

Table 26. Approach to Hypoxemia

Type of Hypoxemia	Settings	$P_aCO_2$	A-a $DO_2$	Oxygen Therapy	Ventilation, BiPAP and PEEP	Improved Cardiac Output
1. Low $F_iO_2$	Postop, high altitude	N or ↓	N	Improves	No change	No change
2. Hypoventilation	Drug overdose	↑	N	Improves	Improves with ventilation	No change
3a. Shunt	ARDS, pneumonia	N or ↓	↑	No change	Improves (except if one-sided)	Improves
3b. Shunt (Right to Left)	Pulmonary HTN	N or ↓	↑	No change	Worsens	Worsens
4. Low mixed venous $O_2$ content	Shock	↓	↑	Improves or no change	Worsens	Improves
5. V/Q mismatch	COPD	N or ↑	↑	Improves (small amounts)	Often improves	Improves
6. Diffusion impairment	ILD, emphysema	N	↑	Improves	Improves with positive pressure	No change or worsens

Reprinted with permission from Dr. Ian Fraser



#### Causes of Hypoxemia

- Low  $F_iO_2$
- Hypoventilation
- Shunting
- Low mixed venous  $O_2$  content
- V/Q mismatch

## Hypercapnic Respiratory Failure

- $P_aCO_2$  increased,  $P_aO_2$  decreased

### Pathophysiology

- increased  $CO_2$  production: fever, sepsis, seizure, acidosis, carbohydrate load
- alveolar hypoventilation: COPD, asthma, CF, chest wall disorder, dead space ventilation (rapid shallow breathing)
  - i.e. inefficient gas exchange results in inadequate  $CO_2$  removal in spite of normal or increased minute volume
- hypoventilation
  - central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (opiates, benzodiazepines)
  - neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis, kyphoscoliosis
  - muscle fatigue

### Treatment

- reverse the underlying pathology
- if  $P_aCO_2 > 50$  mmHg and pH is acidemic consider noninvasive or mechanical ventilation
- correct exacerbating factors
  - NTT/ETT suction: clearance of secretions
  - bronchodilators: reduction of airway resistance
  - antibiotics: treatment of infections
- maintain oxygenation (see above)
- diet: increased carbohydrate can increase  $P_aCO_2$  in those with mechanical or limited alveolar ventilation; high lipids decrease  $P_aCO_2$



#### Dead Space

- Ventilation without perfusion
- The opposite of shunt



#### Causes of Hypercapnia

- High Inspired  $CO_2$
- Low Total Ventilation
- High Deadspace Ventilation
- High  $CO_2$  Production



In chronic hypercapnia, supplemental  $O_2$  may decrease the hypoxic drive to breathe, but do not deny oxygen if the patient is hypoxic.



In COPD patients with chronic hypercapnia ("CO<sub>2</sub> retainers"), provide supplemental oxygen to achieve target  $SpO_2$  from 88-92%.

## Acute Respiratory Distress Syndrome (ARDS)

- clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
- The Berlin Criteria (*JAMA* 2012; 307:2526-2533) for ARDS:
  - acute onset
    - within 7 d of a defined event, such as sepsis, pneumonia, or patient noticing worsening of respiratory symptoms
      - usually occurs within 72 h of presumed trigger
  - bilateral opacities consistent with pulmonary edema on either CT or CXR
  - not *fully* explained by cardiac failure/fluid overload, but patient may have concurrent heart failure
  - an objective assessment (e.g. echocardiogram) should be performed if no clear risk factors

### Etiology

- direct lung injury:
  - airway: aspiration (**gastric contents**, drowning), **pneumonia**, inhalation injury (oxygen toxicity, nitrogen dioxide, smoke)
  - circulation: embolism (fat, amniotic fluid), reperfusion injury
- indirect lung injury
  - circulation: **sepsis**, **shock**, **trauma**, blood transfusion, pancreatitis
  - neurogenic: head trauma, intracranial hemorrhage, drug overdose (narcotics, sedatives, TCAs)

### Pathophysiology

- disruption of alveolar capillary membranes → leaky capillaries → interstitial and alveolar pulmonary edema → reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN

### Clinical Course

#### A. Exudative Phase

- first 7 d of illness after exposure to ARDS precipitant
- alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
- patients develop dyspnea, tachypnea, increased work of breathing
  - these result in respiratory fatigue and eventually respiratory failure (see *Hypoxemic Respiratory Failure*, R25)

#### B. Fibroproliferative Phase

- after day 7
- may still experience dyspnea, tachypnea, fatigue, and hypoxemia
- most patients clinically improve and are able to wean off mechanical ventilation
- some patients develop fibrotic lung changes that may require long-term support on supplemental oxygen or even mechanical ventilation
- if fibrosis present, associated with increased mortality

### Treatment

- based on ARDS network (see *Landmark Respiriology Trials*, R35)
- treat underlying disorder (e.g. antibiotics if infection present)
- mechanical ventilation using low tidal volumes (<6 mL/kg) to prevent barotrauma
  - use optimal amount of PEEP (positive end-expiratory pressure) to keep airways open and allow the use of lower  $F_{iO_2}$
  - may consider using prone ventilation, and/or inhaled nitric oxide, high frequency oscillator or ECMO (extracorporeal membrane oxygenation) if conventional treatment is failing
- fluids and inotropic therapy (e.g. dopamine, vasopressin) if cardiac output inadequate
- pulmonary-arterial catheter now seldom used for monitoring hemodynamics
- mortality: 30-40%, usually due to non-pulmonary complications
- sequelae of ARDS include residual pulmonary impairment, severe debilitation, polyneuropathy and psychologic difficulties, which gradually improve over time
- most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity



**ALI versus ARDS:** Definition is the same, except ALI is a  $P_{aO_2}/F_{iO_2} \leq 300$ , while ARDS is a  $P_{aO_2}/F_{iO_2} \leq 200$



**Categorization of ARDS as Mild, Moderate or Severe – The Berlin Criteria**

ARDS Severity	$P_{aO_2}/F_{iO_2}$ * (mmHg)	Mortality (95% CI)†
Mild	200-300	27 (24-30)%
Moderate	100-200	32 (29-34)%
Severe	<100	45 (42-48)%

\*on  $\geq 5$  cm  $H_2O$  PEEP; †P < 0.001

*JAMA* 2012;307:2526-2533



**Risk Factors for Aspiration Pneumonia**

Categories	Examples
Decreased level of consciousness	Alcoholism
Upper GI tract disorders	Dysphagia, esophageal disorders
Mechanical instrumentation	Intubation, nasogastric tube, feeding tubes
Neurologic conditions	Dementia, Parkinson disease
Others	Protracted vomiting

## Mechanical Ventilation

- see [Anesthesia](#), A10

### Definition

- artificial means of supporting ventilation and oxygenation
- mechanically ventilated patients may require some sedation and/or analgesia



Changes in peak pressures in ACV and tidal volumes in PCV may reflect changes in lung compliance and/or airway resistance – patient may be getting better or worse.

## Indications

- general indications
  - hypoxemic respiratory failure
  - hypercapnic respiratory failure
- specific indicators for mechanical ventilation
  - acute ventilation failure/acute respiratory acidosis
  - refractory hypoxemia
  - reduced level of consciousness
  - facilitation of surgical procedures

## Ventilator Strategies

- mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation
- hypoxemic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

## Modes of Ventilation

- assist-control ventilation (ACV)
  - every breath is delivered with a pre-set tidal volume and rate or minute ventilation
  - extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath
- pressure control ventilation (PCV)
  - a minimum frequency is set and patient may trigger additional breaths above the ventilator
  - all breaths delivered at a preset constant inspiratory pressure
- synchronous intermittent mandatory ventilation (SIMV)
  - ventilator provides controlled breaths (either at a set volume or pressure)
  - patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths
- pressure support ventilation (PSV)
  - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
  - useful for weaning off ventilator
- high-frequency oscillatory ventilation (HFOV)
  - high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes
  - used commonly in neonatal and pediatric respiratory failure
  - used in adults when conventional mechanical ventilation is failing.
- noninvasive positive pressure ventilation (NPPV)
  - achieved without intubation by using a nasal or face mask with:
    - ♦ BiPAP: increased pressure (like PSV) on inspiration and lower constant pressure on expiration
    - ♦ CPAP: delivers constant pressure on both inspiration and expiration

## Complications of Mechanical Ventilation

- airway complications
  - tracheal stenosis, laryngeal edema
- alveolar complications
  - ventilator-induced lung injury, ventilator-associated pneumonia (nosocomial pneumonia), barotrauma, volutrauma, inflammation, auto-PEEP, patient-ventilator asynchrony
- cardiovascular complications
  - reduced venous return, reduced cardiac output, hypotension
- neuromuscular complications
  - muscle atrophy
  - increased intracranial pressure



### Tracheostomy

- Tracheostomy should be considered in patients who require ventilator support for extended periods of time
- Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities



### Positive End Expiratory Pressure (PEEP)

- Positive pressure applied at the end of ventilation which opens up collapsed alveoli decreasing V/Q mismatch
- Used with all invasive modes of ventilation



### Monitoring Ventilatory Therapy

- Pulse oximetry, end-tidal CO<sub>2</sub> concentration
- Regular arterial blood gases
- Assess tolerance regularly



Management of pneumothorax in patients on mechanical ventilation → chest tube.



### A Comparison of Four Methods of Weaning Patients from Mechanical Ventilation

*NEJM* 1995;332:345-350

**Study:** Prospective, randomized, multicenter trial.  
**Participants:** 130 of 546 patients who received mechanical ventilation and were considered ready for weaning but had respiratory distress during a 2 h trial of spontaneous breathing

**Intervention:** One of four weaning techniques following standardized protocol.

**Outcome:** Median duration of weaning.

**Results:** The median duration of weaning for intermittent mandatory ventilation, pressure-support ventilation, intermittent (multiple) trials of spontaneous breathing, and once-daily trial of spontaneous breathing was 5 d, 4 d, and 3 d respectively. The rate of successful weaning was higher with once-daily trial of spontaneous breathing than with intermittent mandatory ventilation (rate ratio 2.83; 95%CI 1.36 to 5.89;  $p < 0.006$ ) or pressure-support ventilation (ratio 2.05; 95%CI 1.04 to 4.04;  $p < 0.04$ ). There was no significant difference in the rate of success between once-daily trials and multiple trials of spontaneous breathing.

**Conclusions:** Once-daily or multiple trials of spontaneous breathing led to extubation more quickly than intermittent mandatory or pressure-support ventilation.

# Neoplasms

## Lung Cancer

### Classification

- lung tumours can be classified as primary or secondary, benign or malignant, endobronchial or parenchymal
- bronchogenic carcinoma (epithelial lung tumours) are the most common type of primary lung tumour (other types make up less than 1%)
  - small cell lung cancer (SCLC)
  - non-small-cell lung cancer (NSCLC)
    - ♦ squamous cell carcinoma: arise from the proximal respiratory epithelium
    - ♦ adenocarcinoma: incidence is increasing; most common subtype in nonsmokers
      - bronchoalveolar carcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring
    - ♦ large cell undifferentiated cancer: diagnosis of exclusion
- benign epithelial lung tumours can be classified as papillomas or adenomas

**Table 27. Characteristics of Bronchogenic Cancer**

Cell Type	Incidence	Correlation with Smoking	Location	Histology	Metastasis
<b>Adenocarcinoma</b>	M: 35% F: 40%	Weak	Peripheral	Glandular, mucin producing	Early, distant
<b>Squamous cell carcinoma (SCC)</b>	30%	Strong	Central	Keratin, intercellular bridges	Local invasion and distant spread, may cavitate
<b>SCLC</b>	25%	Strong	Central	Oat cell, neuroendocrine	Disseminated at presentation Origin in endobronchial cells
<b>Large cell carcinoma</b>	10-15%	Strong	Peripheral	Anaplastic, undifferentiated	Early, distant

**Risk Factors**

- cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers
- other risk factors include cigar smoking, pipe smoking, second-hand smoke, asbestos without smoking (relative risk is 5), asbestos with smoking (relative risk is 92), metals (e.g. chromium, arsenic, nickel), radon gas, ionizing radiation, genetics

**Signs and Symptoms**

- may be due to primary lesion, metastasis, or paraneoplastic syndrome
- primary lesion:
  - cough (75%): beware of chronic cough that changes in character
  - dyspnea (60%)
  - chest pain (45%)
  - hemoptysis (35%)
  - other pain (25%)
  - clubbing (21%)
  - constitutional symptoms: anorexia, weight loss, fever, anemia
- metastasis
  - lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing
  - pericardium: pericarditis, pericardial tamponade
  - esophageal compression: dysphagia
  - phrenic nerve: paralyzed diaphragm
  - recurrent laryngeal nerve: hoarseness
  - superior vena cava syndrome:
    - obstruction of SVC causing neck and facial swelling, as well as dyspnea and cough
    - other symptoms: hoarseness, tongue swelling, epistaxis, and hemoptysis
    - physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton's sign (facial flushing, cyanosis, and distension of neck veins upon raising both arms above head)
    - milder symptoms if obstruction is above the azygos vein
  - lung apex (Pancoast tumour): Horner's syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
  - rib and vertebrae: erosion
  - distant metastasis to brain, bone, liver, adrenals
- paraneoplastic syndromes (see Table 28)
  - a group of disorders associated with malignant disease, not related to the physical effects of the tumour itself
  - most often associated with SCLC

**Table 28. Paraneoplastic Syndromes**

System	Clinical Presentation	Associated Malignancy
<b>Skeletal</b>	Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)	NSCLC
<b>Dermatologic</b>	Acanthosis nigricans Dermatomyositis	Bronchogenic cancer Bronchogenic cancer
<b>Endocrine</b>	Hypercalcemia (osteolysis or PTHrP) Hypophosphatemia Hypoglycemia Cushing's syndrome (ACTH) Somatostatinoma syndrome SIADH	Squamous cell cancer Squamous cell cancer Sarcoma SCLC Bronchial carcinoid SCLC
<b>Neuromyopathic</b>	Lambert-Eaton syndrome Polymyositis Subacute cerebellar degeneration Spinocerebellar degeneration Peripheral neuropathy	SCLC
<b>Vascular/ Hematologic</b>	Nonbacterial endocarditis Trousseau's syndrome (migratory thrombophlebitis) DIC	Bronchogenic cancer NSCLC
<b>Renal</b>	Nephrotic syndrome	

**Summary of Recommendations on Screening for Lung Cancer****Canadian Task Force on Preventive Health Care (2003)****Screening with CXR**  
Not recommended**Screening with low-dose CT**  
Insufficient evidence to make recommendation**American College of Chest Physicians (2013)****Screening with CXR**  
Not recommended**Screening with low-dose CT**  
Recommended for high-risk patients (current or former smokers quit within last 15 yr, aged 55-74, ≥30 pack-yr smoking Hx)**American Lung Association (2013)****Screening with CXR**  
Not recommended**Screening with low-dose CT**  
Recommended for high-risk patients (current or former smokers aged 55-74, ≥30 pack-yr smoking Hx, no Hx of lung cancer)**Reduced Lung-cancer Mortality with Low-dose CT Screening**

NEJM 2011;365:395-409  
Study: Multicenter, RCT.

**Methods:** 53,454 participants at high risk for lung cancer (55-74 yr, >30 yr smoking, and smoking cessation for <5 yr) were assigned to undergo three annual screenings with either low dose CT or single-view PA CXR.

**Results:** A relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95%CI, 6.8 to 26.7; p=0.004). Rate of death from any cause was reduced in the low-dose CT group as compared to the CXR group by 6.7% (95%CI, 1.2 to 13.6; p=0.02).

	Low-dose CT	CXR
Rate of positive screening test	24.2%	6.9%
False positives	96.4%	94.5%
Incidence of lung cancer	645/100K person yr	572/100K person yr
Deaths from lung cancer	247/100K person yr	309/100K person yr

**Conclusions:** Screening with low-dose CT reduces mortality from lung cancer.



Malignant lung tumours are the most common cause of cancer mortality throughout the world in both men and women.

**Endobronchial Ultrasound (EBUS):**

- Allows visualization of peri-bronchial structures and distal peripheral lung lesions
- Provides detailed assessment of the airway wall layers
- Allows for guided biopsies of lymph nodes and tumours
- Used for diagnosis and staging

## Investigations

- initial diagnosis
  - imaging: CXR, CT chest + upper abdomen, PET scan, bone scan
  - cytology: sputum
  - biopsy: bronchoscopy, percutaneous mediastinoscopy
- staging work-up
  - TMN staging system: T – primary tumour (size); N – regional lymph nodes; M – distant metastasis
  - blood work: electrolytes, LFTs, calcium, ALP
  - imaging: CXR, CT thorax and upper abdomen, bone scan, neuroimaging
  - invasive: bronchoscopy (EBUS), mediastinoscopy, mediastinotomy, thoracotomy

**Table 29. SCLC vs. NSCLC**

	Stage	Definition	Treatment	Median Survival
<b>SCLC</b>	Limited stage	Confined to single radiation port (one hemithorax and regional lymph nodes)	Radiation ± chemo ± prophylactic to brain	1-2 yr (12 wk without treatment)
	Extensive stage	Extension beyond a single radiation port	Chemotherapy	6 mo (5 wk without treatment)
	Stage	TNM	Treatment	5 Yr Survival (%)*
<b>NSCLC</b>	IA	T1a-1bN0M0	1st line is complete surgical resection with possible post-op adjuvant chemotherapy with stage IB and stage II. Radiotherapy for non-surgical candidates.	50-73
	IB	T2aN0M0		43-58
	IIA	T1a-T2a,N1M0 or T2bN0M0		36-46
	IIB	T2bN1M0 or T3N0M0	Combined modality approach (concurrent chemotherapy followed by surgery)	25-36
	IIIA	T1a-T2bN2M0 or T3N1-2M0 or T4N0-1M0		19-24
	IIIB	T4N2M0 or T1-4N3M0		7-9
	IV	T1-4N0-3M1a-1b	Systemic therapy or molecularly targeted therapy or symptom-based palliative management (radiation). Isolated metastasis may be resected.	2-13

\* Depends on clinical vs. pathologic stage

Refer to *AJCC Cancer Staging Manual*, 7th ed. (2010) for complete TNM classification

## Treatment

- options include surgery, radiotherapy, chemotherapy, and palliative care for end-stage disease (see Table 29)
- surgery not usually performed for SCLC since it is generally non-curable
- contraindications for surgery:
  - spread to contralateral lymph nodes or distant sites
    - patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
  - poor pulmonary status (e.g. unable to tolerate resection of lung)
- chemotherapy (used in combination with other treatments)
  - common agents: etoposide, platinum agents (e.g. cisplatin), ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  - complications:
    - acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
    - chronic: neurologic damage, leukemia, additional primary neoplasms

## Prognosis

- 5 yr survival rates for different subtypes:
  - squamous cell carcinoma 25%
  - adenocarcinoma 12% (60% for bronchoalveolar carcinoma, a subtype of adenocarcinoma, with a resectable solitary lesion)
  - large cell carcinoma 13%
  - SCLC 1% (poorest prognosis)
  - NSCLC (see Table 29)

## Prevention

- smoking cessation
- avoidance of exposures
- early detection



### Horner has a MAP of the Coast

A Pancoast tumour compresses the cervical sympathetic plexus causing a Horner's syndrome:

Miosis  
Anhydrosis  
Ptosis



2/3 of primary lung cancer is found in the upper lung; 2/3 of metastases occur in the lower lung (hematogenous spread secondary to increased blood flow to the base of the lung).



Combination treatment may be superior, giving better response rates.



## Approach to the Solitary Pulmonary Nodule

- also see [Medical Imaging](#), MI7

### Definition

- a round or oval, sharply circumscribed radiographic lesion up to 3-4 cm, which may or may not be calcified, and is surrounded by normal lung
- can be benign or malignant

**Table 30. Differential Diagnosis for Benign vs. Malignant Solitary Nodule**

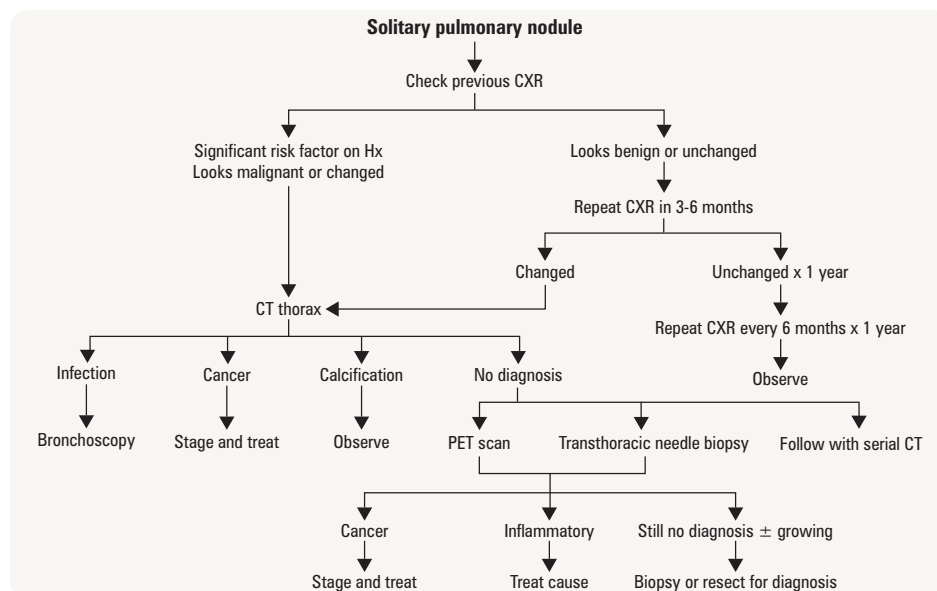
Benign (70%)	Malignant (30%)
<b>Infectious granuloma</b> (histoplasmosis, coccidiomycosis, TB, atypical mycobacteria) <b>Other infections</b> (bacterial abscess, PCP, aspergilloma) <b>Benign neoplasms</b> (hamartoma, lipoma, fibroma) <b>Vascular</b> (AV malformation, pulmonary varix) <b>Developmental</b> (bronchogenic cyst) <b>Inflammatory</b> (granulomatosis with polyangiitis, rheumatoid nodule, sarcoidosis) <b>Other</b> (hematoma, infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma, hamartoma)	<b>Bronchogenic carcinoma</b> Adenocarcinoma Squamous cell carcinoma Large cell carcinoma Small cell carcinoma <b>Metastatic lesions</b> Breast Head and neck Melanoma Colon Kidney Sarcoma Germ cell tumours <b>Pulmonary carcinoid</b>

### Investigations (see Figure 11)

- CXR: always compare with previous CXR (see Table 31)
- CT densitometry and contrast enhanced CT of thorax
- sputum cytology: usually poor yield
- biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy or thoracotomy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  - if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  - if a biopsy is non-diagnostic, whether to observe, re-biopsy or resect will depend on the level of suspicion
- watchful waiting: repeat CXR and/or CT scan at 3, 6, 12 mo
- PET scan can help distinguish benign from malignant nodules

**Table 31. CXR Characteristics of Benign vs. Malignant Solitary Nodule**

Parameters	Benign	Malignant
<b>Size</b>	<3 cm, round, regular	>3 cm, irregular, spiculated
<b>Margins</b>	Smooth margin	Ill-defined or notched margin
<b>Features</b>	Calcified pattern: central, "popcorn" pattern if hamartoma, usually no cavitation; if cavitated, wall is smooth and thin, no other lung pathology	Usually not calcified; if calcified, pattern is eccentric, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy
<b>Doubling Time</b>	Doubles in <1 mo or >2 yr	Doubles in >1 mo or <2 yr



**Figure 11. Evaluation of a solitary pulmonary nodule**



### Carcinoids

- Early onset (40-60 yr)
- Most are central and can produce symptoms and signs of bronchial obstruction
- Hemoptysis is present in approximately 50% of cases



### Hamartomas

- 10% of benign lung lesions
- Composed of tissues normally present in lung (fat, epithelium, fibrous tissue and cartilage), but they exhibit disorganized growth
- Peak incidence is age 60, more common in men
- Usually peripheral and clinically silent
- CXR shows clustered "popcorn" pattern of calcification (pathognomonic for hamartoma)



Pulmonary neoplasms may present as a solitary pulmonary nodule identified incidentally on a radiographic study (~10% of cases) or as symptomatic disease (most cases).



Adenocarcinoma present in a non-smoker is usually due to endothelial growth factor receptor mutation.



### Corona Radiata Sign on Chest CT

- Fine striations that extend linearly from a nodule in a spiculated fashion
- Highly associated with malignancy



### Terminology

- "nodule" <3 cm
- "mass" >3 cm

# Sleep-Related Breathing Disorders

## Hypoventilation Syndromes

- primary alveolar hypoventilation: idiopathic
- obesity-hypoventilation syndrome (Pickwickian syndrome)
- respiratory neuromuscular disorders

## Sleep Apnea

### Definition

- episodic decreases in airflow during sleep
- quantitatively measured by the Apnea/Hypopnea Index (AHI) = # of apneic and hypopneic events per hour of sleep
- sleep apnea generally accepted to be present if AHI >15

### Classification

- obstructive (OSA)
  - caused by transient, episodic obstruction of the upper airway
  - absent or reduced airflow despite persistent respiratory effort
- central (CSA) (see [Neurology](#), N42)
  - caused by transient, episodic decreases in CNS drive to breathe
  - no airflow because no respiratory effort
  - Cheyne-Stokes Respiration: a form of CSA in which central apneas alternate with hyperpneas to produce a crescendo-decrescendo pattern of tidal volume; seen in severe LV dysfunction, brain injury, and other settings (Figure 2)
- mixed (MSA)
  - features of both OSA and CSA
  - loss of hypoxic and hypercapnic drives to breathe secondary to "resuscitative breathing": overcompensatory hyperventilation upon awakening from OSA induced hypoxia

### Risk Factors

- for OSA: obesity, upper airway abnormality, neuromuscular disease, hypothyroidism, alcohol/sedative use, nasal congestion, sleep deprivation
- for CSA: LV failure, brainstem lesions, encephalitis, encephalopathy, myxedema, high altitude

### Signs and Symptoms

- obtain history from spouse/partner
- secondary to repeated arousals and fragmentation of sleep: daytime somnolence, personality and cognitive changes, snoring
- secondary to hypoxemia and hypercapnia: morning headache, polycythemia, pulmonary/systemic HTN, cor pulmonale/CHF, nocturnal angina, arrhythmias
- the typical presentation for OSA is a middle-aged obese male who snores
- CSA can be due to neurological disease

### Investigations

- sleep study (polysomnography)
  - evaluates sleep stages, airflow, ribcage movement, ECG, SaO<sub>2</sub>, limb movements
  - indications
    - ♦ excessive daytime sleepiness
    - ♦ unexplained pulmonary HTN or polycythemia
    - ♦ daytime hypercapnia
    - ♦ titration of optimal nasal CPAP
    - ♦ assessment of objective response to other interventions

### Treatment

- modifiable factors: weight loss, decreased alcohol/sedatives, nasal decongestion, treatment of underlying medical conditions
- OSA or MSA: nasal CPAP, postural therapy (i.e. no supine sleeping), dental appliance, uvulopalatopharyngoplasty, tonsillectomy
- CSA or hypoventilation syndromes: nasal BiPAP/CPAP, respiratory stimulants (e.g. progesterone) in select cases
- tracheostomy rarely required and should be used as last resort for OSA

### Complications

- depression, weight gain, decreased quality of life, workplace and vehicular accidents, cardiac complications (e.g. HTN), reduced work/social function



#### Normal Respiratory Changes during Sleep

- Tidal volume decreases
- Arterial CO<sub>2</sub> increases (due to decreased minute ventilation)
- Pharyngeal dilator muscles relax causing increased upper airway resistance



**Apnea:** absence of breathing for ≥10 s.

**Hypopnea:** excessive decrease in rate or depth of breathing (>50% reduction in ventilation).

**Hyperpnea:** excessive increase in rate or depth of breathing.



#### Continuous Positive Airways Pressure for Obstructive Sleep Apnea

*Cochrane DB Syst Rev 2006;CD001106*

**Study:** Pooled analysis of 36 RCTs (n=1718) comparing nocturnal CPAP with an inactive control or oral appliances in adults with OSA.

**Conclusions:** The use of CPAP showed significant improvements in objective and subjective measures including cognitive function, sleepiness, measures of quality of life, and a lower average systolic and diastolic blood pressure. People who responded equally well to CPAP and oral appliances expressed a strong preference for oral appliances; however, participants on oral appliances were more likely to withdraw from therapy.



CPAP has been shown to reduce cardiovascular risk and cardiovascular related deaths in patients with obstructive sleep apnea.

## Introduction to Intensive Care

- goal is to provide stabilization for critically ill patients: hemodynamic, respiratory or cardiac instability, or need for close monitoring

### ICU Basics

#### Lines and Catheters

- arterial lines
  - monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs
  - common sites are the radial and femoral arteries
- central venous catheter (central line)
  - administer IV fluids, monitor CVP, insert pulmonary artery catheters
  - administer TPN and agents too irritating for peripheral line
  - common sites: internal jugular vein, subclavian vein, femoral vein
- pulmonary arterial catheter
  - balloon guides the catheter from a major vein to the right heart
  - measures pulmonary capillary wedge pressure (PCWP) via a catheter wedged in distal pulmonary artery
  - PCWP reflects the LA and LV diastolic pressure (barring pulmonary venous or mitral valve disease)
  - indications (N.B. now used infrequently due to associated complications):
    - ♦ diagnosis of shock states, primary pulmonary HTN, valvular disease, intracardiac shunts, cardiac tamponade, PE
    - ♦ assessment of hemodynamic response to therapies
    - ♦ differentiation of high- versus low-pressure pulmonary edema
    - ♦ management of complicated MI, multiorgan system failure and/or severe burns, or hemodynamic instability after cardiac surgery
  - absolute contraindications:
    - ♦ tricuspid or pulmonary valve mechanical prosthesis
    - ♦ right heart mass (thrombus or tumour)
    - ♦ tricuspid or pulmonary valve endocarditis

**Table 32. Useful Equations and Cardiopulmonary Parameters**

$BSA = [Ht (cm) + Wt (kg) - 60]/100$	$PCWP = LVEDP$
$SV = CO / HR$	$SVI = CI / HR$
$CI = CO / BSA$	$RV \text{ Ejection Fraction} = SV / RVEDV$
$SVRI = [(MAP - RAP) 80]/CI$	$PP = sBP - dBP$
$P:F \text{ ratio} = P_{aO_2} / F_{iO_2}$	$MAP = 1/3 sBP + 2/3 dBP = dBP + 1/3 PP$

BSA = body surface area; CI = cardiac index; CO = cardiac output; DBP = diastolic blood pressure; HR = heart rate; LVEDP = left ventricular end diastolic pressure; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; PP = pulse pressure; RAP = right atrial pressure; RVEDV = right ventricular end diastolic volume; SBP = systolic blood pressure; SV = stroke volume; SVI = stroke volume index; SVRI = systemic vascular resistance index



#### ICU Psychosis

A form of delirium or acute brain failure that occurs in ICU patients. Signs and symptoms may include anxiety, agitation, paranoia, hallucinations, and disorientation in time and place. Treatment varies with cause.



#### Intensive Insulin Therapy in Critically Ill Patients

NEJM 2001;345:1359-1367

**Study:** Prospective, randomized controlled clinical outcome study.

**Patients:** 1548 patients admitted to the ICU.

**Intervention:** At admission, patients were randomly assigned to either intensive insulin therapy or conventional therapy. Those in the intensive group had an infusion started if BG exceeded 6.1 mmol/L, and maintained to keep BG between 4.4 to 6.1 mmol/L.

Those in the conventional group were started on insulin only if BG exceeded 11.9, and the infusion was adjusted for a target between 10.0 and 11.1 mmol/L.


**Primary Outcome:** Death from any cause during ICU stay.

**Results:** 35 patients (4.6%) died in the intensive group in the ICU, versus 63 patients (8.0%) in the conventional group. This represents a 32% mortality reduction ( $p=0.04$ ). Intensive insulin therapy also reduced overall in-hospital mortality, lowered deaths due to sepsis, multi-organ failure. Most of the mortality benefit was seen in long stay patients ( $>5$  d).

**Conclusion:** Intensive insulin therapy in the ICU reduces mortality by 32%, and improves in-hospital mortality and morbidity.

## Organ Failure

**Table 33. Types of Organ Failure**

Type of Failure	Clinical Presentation	Treatment
<b>Respiratory Failure</b> (see <i>Respiratory Failure</i> , R24)	Hypoxemia Hypercapnea	Treat underlying cause (e.g. lung disease, shunt, V/Q mismatch, drug-related, cardiac) Manage mechanical ventilation settings Supplemental oxygen
<b>Cardiac Failure</b> (see <i>Cardiology</i> , C30) 	Hypotension Decreased urine output Altered mental status Arrhythmia Hypoxia	Treat underlying cause (e.g. bradycardia, tachycardia, blood loss, adrenal insufficiency) Volume resuscitation Vasopressors Inotropes Intra-aortic balloon pump
<b>Coagulopathy</b> (see <i>Hematology</i> , H34)	Increased INR or PTT Low platelet count Bleeding, bruising	Treat underlying cause (e.g. thrombocytopenia, drug-related, immune-related, DIC) Transfusion of blood product, clotting factors
<b>Liver Failure</b> (see <i>Gastroenterology</i> , G36)	Elevated transaminases, bilirubin Coagulopathy Jaundice Mental alteration (encephalopathy) Hypoglycemia	Treat underlying cause (e.g. viral hepatitis, drug related, metabolic) Liver transplant Lactulose
<b>Renal Failure</b> (see <i>Nephrology</i> , NP35)	Elevated creatinine Reduced urine output Signs of volume overload (e.g. CHF, effusions)	Treat underlying cause (e.g. shock, drug-related, obstruction) Correct volume and electrolyte status, eliminate toxins Diuretics Dialysis

## Shock

- see [Emergency Medicine](#), ER3
- inadequate tissue perfusion potentially resulting in end organ injury
  - categories of shock:
    - ♦ hypovolemic: hemorrhage, dehydration, vomiting, diarrhea, interstitial fluid redistribution
    - ♦ cardiogenic: myopathic (myocardial ischemia ± infarction), mechanical, arrhythmic, pharmacologic
    - ♦ obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
    - ♦ distributive: sepsis, anaphylactic reaction, neurogenic, endocrinologic, toxic



**Table 34. Changes Seen in Different Classes of Shock**

	Hypovolemic	Cardiogenic	Obstructive	Distributive
HR	↑	↑, N, or ↓	↑	↑
BP	↓	↓	↓	↓
JVP	↓	↑	↑	↓
Extremities	Cold	Cold	N or Cold	Warm
Other	Look for visible hemorrhage or signs of dehydration	Bilateral crackles on chest exam	Depending on cause, may see pulsus paradoxus, Kussmaul's sign, or tracheal deviation	Look for obvious signs of infection or anaphylaxis

- treat underlying cause
- treatment goal is to return critical organ perfusion to normal (e.g. normalize BP)
- common treatment modalities include:
  - fluid resuscitation
  - inotropes (e.g. dobutamine), vasopressors (e.g. norepinephrine), vasopressin
  - revascularization or thrombolytics for ischemic events



### Shock: Clinical Correlation

**Hypovolemic:** patients have cool extremities due to peripheral vasoconstriction.

**Cardiogenic:** patients usually have signs of left-sided heart failure.

**Obstructive:** varied presentation.

**Distributive:** patients have warm extremities due to peripheral vasodilation.



### Causes of SHOCK

Spinal (neurogenic), Septic Hemorrhagic

**Obstructive** (e.g. tension pneumothorax, cardiac tamponade, PE)

**Cardiogenic** (e.g. arrhythmia, MI) **Anaphylactic**

## Sepsis

- the leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- the predominant theory is that sepsis is attributable to uncontrollable immune system activation

### Definitions

- sepsis: the presence of both infection and SIRS (see Table 35)
- severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension
- septic shock: sepsis with arterial hypotension despite adequate fluid resuscitation
- multiorgan dysfunction syndrome: sepsis in the presence of altered organ function such that homeostasis cannot be maintained without intervention

### Signs and Symptoms

**Table 35. Clinical Manifestations of Sepsis**

General Variables	Organ Dysfunction Variables
Fever ( $>38^{\circ}\text{C}$ ) or hypothermia ( $<36^{\circ}\text{C}$ )	Arterial hypoxemia ( $\text{P}_{\text{a}}\text{O}_2/\text{F}_{\text{O}_2} <300$ )
Heart rate $>90/\text{min}$	Acute oliguria (urine output $<0.5\text{ mL/kg/h}$ )
sBP $<90\text{ mmHg}$ , MAP $<70$ , or a sBP decrease $>40\text{ mmHg}$	Creatinine increase $>0.5\text{ mg/dL}$
Tachypnea	Coagulation abnormalities (INR $>1.5$ or aPTT $>60\text{ s}$ )
Altered mental status	Ileus (absent bowel sounds)
Positive fluid balance ( $>20\text{ mL/kg}$ over 24 h)	Thrombocytopenia (platelet count $<100,000/\text{L}$ )
Hyperglycemia (BG $>7.7\text{ mmol/L}$ ) in the absence of diabetes	Hyperbilirubinemia (plasma total bilirubin $>4\text{ mg/dL}$ or $70\text{ mmol/L}$ )
Leukopenia (WBC $<4,000/\text{L}$ )	Leukocytosis (WBC $>12,000/\text{L}$ )
Normal WBC count with $>10\%$ immature forms	
Plasma C-reactive protein $>2\text{ SD}$ above the normal value	
	<b>Tissue Perfusion Variables</b>
	Hyperlactatemia ( $>1\text{ mmol/L}$ )
	Decreased capillary refill or mottling

Table adapted with permission from Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent J-L, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Critical Care Medicine 2003;31:1250-1256

### Treatment

- identify the cause and source of infection: blood, sputum, urine Gram stain and C&S
- initiate empiric antibiotic therapy
- monitor, restore and maintain hemodynamic function

### Early Goal Directed Therapy

- adjustments of cardiac preload, afterload and contractility to balance oxygen delivery with demand
- should be started immediately and completed within 6 h of recognition of severe sepsis or septic shock



### Systemic Inflammatory Response Syndrome (SIRS):

generalized inflammatory reaction caused by infectious and noninfectious entities, manifested by two or more of:

- Body temperature  $>38.5^{\circ}\text{C}$  or  $<35^{\circ}\text{C}$
- Heart rate  $>90/\text{min}$
- Respiratory rate  $>20/\text{min}$  or  $\text{P}_{\text{a}}\text{CO}_2 <32\text{ mmHg}$
- WBC  $>12,000\text{ cells/mL}$  or  $<4,000\text{ cells/mL}$  or  $>10\%$  bands



### Corticosteroids for Treating Severe Sepsis and Septic Shock

*Cochrane DB Syst Rev* 2010;CD002243

**Study:** Meta-analysis of 25 RCTs and quasi-RCTs examining the efficacy of corticosteroids on death at one month in patients with severe sepsis and septic shock.

**Results:** Overall, there was no difference in 28-d all-cause mortality but there was significant heterogeneity in dosing strategy between the studies. Treatment with long course of low dose corticosteroids significantly reduced 28-d mortality, increased the proportion of shock reversal by day 7 and day 28, reduced the sepsis-related organ failure assessment score by day 7, and survivors' length of stay in the ICU, without inducing gastrointestinal bleeding, superinfection, or neuromuscular weakness. Corticosteroids increased the risk of hyperglycemia and hypernatremia.

**Conclusions:** Corticosteroids did not change mortality in severe sepsis and septic shock. A long course of low dose corticosteroids reduced 28-d mortality without major complications.

- patient should meet SIRS criteria and sBP <90 mmHg or lactate >4 mmol/L
  1. supplemental oxygen ± intubation and mechanical ventilation
  2. central venous and arterial catheterization
  3. maintain CVP 8-12 mmHg with IV crystalloids/colloids
  4. MAP maintained 65-90 mmHg with the use of vasoactive agents
  5.  $S_{cv}O_2$  <70% then
    - ♦ transfusion of red cells until Hct >30%
    - ♦ if  $S_{cv}O_2$  <70% after transfusion then use inotropic agents
- supportive oxygenation and ventilation using lung-protective regimen
- early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier
- control hyperglycemia with insulin to decrease infectious complications
- physiologic dose corticosteroid replacement therapy in patients with relative adrenal insufficiency (nonresponders to corticotropin stimulation test)
  - consider in mechanically ventilated septic shock patients with organ dysfunction requiring vasopressors, despite early goal-directed therapy and appropriate antibiotic therapy
- recombinant activated protein C may be considered in patients with severe sepsis or septic shock with an APACHE II score >25 despite early goal-directed therapy and appropriate antibiotic therapy
- DVT/PE prophylaxis
- advanced care planning, including the communication of likely outcomes and realistic goals of treatment with patients and families



#### Early Goal-Directed Therapy for Severe Sepsis and Septic Shock

NEJM 2001;345:1368-1377

**Purpose:** To evaluate the efficacy of early goal-directed therapy before ICU admission.

**Methods:** Randomized assignment of patients who presented to emergency with severe sepsis or septic shock to either 6 h of early goal-directed therapy or standard therapy (hemodynamic support protocol). Clinicians who assumed care subsequently were blinded to treatment assignment. Primary outcomes were mortality and APACHE II scores.

**Results:** The mortality rate in the early therapy group (n=130) and control group (n=133) was 30.5% and 46.5% respectively (p=0.009). Within the 72 h, early therapy resulted in a significantly higher mean central venous oxygen saturation (70.4% vs. 65.3%), a lower lactate concentration (3.0 vs. 3.9 mmol/L), and a higher pH (7.40 vs. 7.36) compared to standard therapy (P<0.02 for all comparisons). APACHE II scores were significantly lower in the early therapy group (13.0 vs. 15.9; P<0.001).

**Conclusion:** Severe sepsis and septic shock significantly benefit from early goal-directed therapy compared to standard therapy protocols.

## Common Medications

Table 36. Common Medications for Respiratory Diseases

	Drug	Typical Adult Dose	Indications	Side Effects
<b>β<sub>2</sub>-AGONISTS</b>				
<b>Short-acting</b>	salbutamol/albuterol (Ventolin®) (light blue/navy), terbutaline (Bricanyl®)	1-2 puffs q4-6h prn	Bronchodilator in acute reversible airway obstruction	CV (angina, flushing, palpitations, tachycardia, can precipitate Afib), CNS (dizziness, headache, insomnia, anxiety), GI (diarrhea, nausea, vomiting), rash, hypokalemia, paroxysmal bronchospasm
<b>Long-acting</b>	salmeterol (Serevent®), formoterol (Oxeze®) indacaterol (Onbrez®)	1-2 puffs bid 1 puff daily	Maintenance treatment (prevention of bronchospasm) in COPD, asthma	
<b>Combination Long-acting β<sub>2</sub>-agonist and inhaled corticosteroid</b>	fluticasone and salmeterol (Advair®) (purple MDI or diskus) Budesonide and formoterol (Symbicort®) (red turbuhaler) Mometasone and formoterol (Zenhale®) (blue MDI)	1 puff bid 2 puffs bid	COPD and asthma	Common: CNS, headache, dizziness Resp: URTI, GI (N/V, diarrhea, pain/discomfort, oral candidiasis)
<b>ANTICHOLINERGICS</b>				
	ipratropium bromide (Atrovent®) (clear/green), tiotropium bromide (Spiriva®) glycopyrronium bromide	2-3 puffs qid 1 puff qam 1 puff daily	Bronchodilator used in COPD, bronchitis and emphysema	Palpitations, anxiety, dizziness, fatigue, headache, nausea, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs
<b>CORTICOSTEROIDS</b>				
<b>Inhaled</b>	fluticasone (Flovent®) (orange/peach) budesonide (Pulmicort®) ciclesonide (Alvesco®) beclomethasone (QVAR®, Vanceril®) Mometasone (Asmanex®)	2-4 puffs bid 2 puffs bid 1-4 puffs OD 1-4 puffs bid (40 µg), 1-2 puffs bid (80 µg) 1 puff daily or bid	Maintenance treatment of asthma	Headache, fever, N/V, MSK pain, URTI, throat irritation, growth velocity reduction in children/adolescents, HPA axis suppression, increased pneumonia risk in COPD
<b>Systemic</b>	prednisone (Apo-prednisone®, Deltasone®) methylprednisolone (Depo-Medrol®, Solu-Medrol®)	Typically 40-60 mg per day PO 125 mg q8h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q6h for 5 d	Acute exacerbation of COPD; severe, persistent asthma, PCP Status asthmaticus	Endocrine (hirsutism, DM/glucose intolerance, Cushing's syndrome, HPA axis suppression), GI (increased appetite, indigestion), ocular (cataracts, glaucoma), edema, AVN, osteoporosis, headache, psych (anxiety, insomnia), easy bruising
<b>ADJUNCT AGENTS</b>				
	theophylline (Uniphyll®)	400-600 mg OD	Treatment of symptoms of reversible airway obstruction due to COPD	GI upset, diarrhea, N/V, anxiety, headache, insomnia, muscle cramp, tremor, tachycardia, PVCs, arrhythmias, Toxicity: persistent, repetitive vomiting, seizures
<b>LEUKOTRIENE ANTAGONISTS</b>				
	montelukast (Singulair®) zafirlukast (Accolate®)	10 mg PO qhs, now only available as once daily slow release 20 mg bid	Prophylaxis and chronic treatment of asthma	Headache, dizziness, fatigue, fever, rash, dyspepsia, cough, flu-like symptoms
<b>MONOCLONAL ANTIBODIES</b>				
	omalizumab (Xolair®)	150-375 mg SC q2-4wk	Moderate-severe persistent asthma	Headache, sinusitis, pharyngitis, URTI, viral infection, thrombocytopenia, anaphylaxis



**Table 36. Common Medications for Respiratory Diseases** (continued)

Table 69: Common Medications for Respiratory Diseases (continued)				
	Drug	Typical Adult Dose	Indications	Side Effects
PDE5 INHIBITORS				
	Roflumilast (Daxas®)	500 µg PO OD	Severe emphysema, with frequent exacerbations	Weight loss, suicidal ideation
ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA				
Macrolide	erythromycin	250-500 mg PO tid x 7-10 d	Alternate to doxycycline or fluoroquinolone	GI (abdominal pain, diarrhea, N/V), headache, prolonged QT, ventricular arrhythmias, hepatic impairment GI (diarrhea, N/V, abdo pain), renal failure, deafness Headache, rash, GI (diarrhea, N/V, abnormal taste, heartburn, abdo pain), increased urea
	azithromycin	500 mg PO x 1 dose, then 250 mg OD x 4		
	clarithromycin	500 mg PO bid x 7-10 d		
Doxycycline		100 mg PO bid x 7-10 d	Alternate to macrolide or fluoroquinolone	Photosensitivity, rash, urticaria, anaphylaxis, diarrhea, enterocolitis, tooth discolouration in children
Fluoroquinolone	levofloxacin (Levaquin®)	500 mg PO OD x 7-10 d	Alternate to macrolide or doxycycline	CNS (dizziness, fever, H/A), GI (N/V, diarrhea, constipation), prolonged QT
	moxifloxacin (Avelox®)	400 mg PO OD x 7 d		
ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA				
3rd gen Cephalosporin	ceftriaxone (Rocephin®)	1-2 g IV OD x 7-10 d	Combine with fluoroquinolone or macrolide	Rash, diarrhea, eosinophilia, thrombocytosis, leukopenia, elevated transaminases
Fluoroquinolone	levofloxacin	750 mg PO OD x 5 d	Combine with 3rd gen cephalosporin	See above
	moxifloxacin	400 mg PO OD x 7 d (5 d for AECOPD)		
Piperacillin/Tazobactam (Tazocin®)		4.5 g IV q6-8h x 7-10 d	Suspect Pseudomonas	CNS (confusion, convulsions, drowsiness), rash, Hematologic (abnormal platelet aggregation, prolonged PT, positive Coombs)
Vancomycin (Vancocin®)		1 g IV bid x 7-10 d	Suspect MRSA	CNS (chills, drug fever), hematologic (eosinophilia), rash, red man syndrome, interstitial nephritis, renal failure, ototoxicity
Macrolide	azithromycin	500 mg IV OD x 2 d, then 500 mg PO OD x 5 d	Suspect Legionella	See above See above
	clarithromycin	500 mg PO bid x 7-10 d		
ICU MEDICATIONS				
Pressors/Inotropes	norepinephrine (Levophed®)	0.5-30 µg/min IV	Acute hypotension	Angina, bradycardia, dyspnea, hyper/hypotension, arrhythmias
	phenylephrine	0.5 µg/kg/min IV	Severe hypotension	See above
	dobutamine	2-20 µg/kg/min IV	Inotropic support	See above
Sedatives/Analgesia	fentanyl (opioid class)	50-100 µg then 50-unlimited µg/h IV	Sedation and/or analgesia	Bradycardia, respiratory depression, drowsiness, hypotension
	propofol (anesthetic)	1-3 mg/kg then 0.3-5 mg/kg/h IV	Sedation and/or analgesia	Apnea, bradycardia, hypotension (good for ventilator sedation)

See [Infectious Diseases](#), ID23 – for the management of pulmonary tuberculosis

## Landmark Respiriology Trials

Trial	Reference	Results
ARDS Network	NEJM 2000; 342:1301-8	Mortality decreased in ARDS patients ventilated with a low tidal volume strategy
Berlin Criteria	JAMA 2012; 307:2526-33	The new definition of ARDS, better predicts mortality
CPAP and Apnea	NEJM 2005; 353:2025-33	CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF
EINSTEIN-PE	NEJM 2012; 366:1287-97	Fixed dose of rivoxaban was non-inferior to standard therapy (Vit K antagonist) initial and long term treatment of PE
Emphysema Treatment Trial	NEJM 2003; 348:2059-73	Lung volume reduction surgery benefits patients with upper lobe disease and low exercise capacity
IELCAP	NEJM 2006; 355:1763-71	High survival rate in patients with early stage lung cancer detected by low dose CT screening
Lung Health	JAMA 1994; 272:1497-505	Aggressive smoking intervention significantly decreases the age-related decline in FEV <sub>1</sub> in middle-aged smokers with mild airways obstruction
Pneumonia	NEJM 1978; 298:801-9	Interstitial lung disease subsets have different prognoses and response to treatment (e.g. desquamative but not usual interstitial pneumonia respond well to corticosteroids)
POET-COPD	NEJM 2011; 364:1093-103	Tiotropium decreases the number of moderate-to-severe exacerbations in comparison to salmeterol
ROFLUMILAST	LANCET 2009; 374:695-703	Leukotriene inhibitors improve FEV <sub>1</sub> when used as add-on therapy in COPD patients on tiotropium or salmeterol
TORCH	NEJM 2007; 356:775-89	Combination of inhaled steroids and long-acting β <sub>2</sub> -agonists improves COPD symptoms, reduces exacerbations and shows a trend to lowers mortality
UPLIFT	NEJM 2008; 359:1543-54	Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect FEV <sub>1</sub> decline



# References

- Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *NEJM* 2003;348:2618-2625.
- Andreoli TE. *Cecil essentials of medicine*, 8th ed. Philadelphia: WB Saunders, 2010.
- Anane D, Belissant E, Bollaert PE, et al. Corticosteroids for treating severe sepsis and septic shock. *Cochrane DB Syst Rev* 2004;1:CD002243.
- ARDS Definition Task Force, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA* 2012;307:2526-2533.
- Augustino P, Ouriel K. Invasive approaches to treatment of venous thromboembolism. *Circulation* 2004;110(suppl 1):1-27-1-34.
- Bach PB, Brown C, Gelfand SE. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. *Ann Int Med* 2001;34:600-620.
- Bach PB, Silvestri GA, Hanger M, Jett JR. Screening for lung cancer: ACCP evidence-based clinical practice guidelines, 2nd ed. *Chest* 2007;132:695-775.
- Badesh, et al. Medical therapy for pulmonary arterial hypertension. ACCP evidence-based clinical practice guidelines. *Chest* 2004;126(1 Suppl):35S-62S.
- Balk RA. Optimum treatment of severe sepsis and septic shock: evidence in support of the recommendations. *Disease-A-Month* 2004;50:168-213.
- Bartlett JG, Dowell SF, Mandell LA, et al. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000;31:347-382.
- Bass JB Jr, Fierer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. *Am J Respir Crit Care Med* 1994;149:1359-1374.
- Baumann MH. Treatment of spontaneous pneumothorax. *Curr Opin Pulm Med* 2000;Jul;6:275-280.
- Boulet LP, Becker A, Berube D, et al. Canadian asthma consensus report. *CMAJ* 1999;161(11Suppl):S1-61.
- Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2004;126:401S-428S.
- Chunilal SD, Eikelboom JW, Attia J, et al. Dose this patient have pulmonary embolism? *JAMA* 2003;290:2849-2858.
- Crapo JD, Glassroth JL, Karlinsky JB, Talmadge EK. *Baum's textbook of pulmonary diseases*, 7th ed. USA: Lippincott Williams & Wilkins, 2003.
- Delinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004;32:536-555.
- Esteban A, Frutos F, Tobin M, et al. A comparison of four methods of weaning patients from mechanical ventilation. *NEJM* 1995;332:345-350.
- Ferguson GT, Cherniack RM. Management of chronic obstructive pulmonary disease. *NEJM* 1993;328:1017-1022.
- Ferri F. *Ferri's clinical advisor*. Mosby/Elsevier Health Sciences, 2002.
- Ferri F. *Practical guide to the care of the medical patient*, 5th ed. St.Louis: Mosby/Elsevier Sciences, 2001.
- File TM. The epidemiology of respiratory tract infections. *Semin Respir Infect* 2000;15:184-194.
- Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *NEJM* 1997;336:243-250.
- Gain S. Pulmonary hypertension. *JAMA* 2000;284:3160-3168.
- Garcia D, Ageno W, Libby E. Update on the diagnosis and management of pulmonary embolism. *Brit J Haematol* 2005;131:301-312.
- Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism. *Chest* 2004;126:338S-400S.
- Giles TL, Lasserson TJ, Smith BJ, et al. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane DB Syst Rev* 2006;5:CD001106.
- Gorecka et al. Effect of long term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 1997;52:674-679.
- Gotfried M, Freeman C. An update on community-acquired pneumonia in adults. *Compr Ther* 2000;26:283-293.
- Green DS, San Pedro GS. Empiric therapy of community-acquired pneumonia. *Semin Respir Infect* 2000;15:227-233.
- Hershfield E. Tuberculosis: treatment. *CMAJ* 1999;161:405-411.
- Holleman D, Simel D. Does the clinical examination predict airflow limitation? *JAMA* 1995;273:313-319.
- Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *NEJM* 2003;348:138-150.
- Idiopathic Pulmonary Fibrosis Clinical Research Network, Raghu G, Anstrom KJ, King TE Jr, Lasky JA, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *NEJM* 2001;366:1968-1977.
- Kasper DL, Braunwald E, Fauci AS, et al (editors). *Harrison's principles of internal medicine*, 16th ed. USA: McGraw-Hill Professional, 2004.
- Kline JA, Courtney DM, Kabriel C, Moore CL, Smithline HA, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6:772-780.
- Lexi-Comp Inc. (Lexi-Drugs (Comp + Specialties™)) Lexi-Comp Inc, Oct.12, 2002 version.
- Light RW, Macgregor MI, Luchsinger PC, et al. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med* 1972;77:507-513.
- Light RW. The management of parapneumonic effusions and empyema. *Curr Opin Pulm Med* 1998;4:227-229.
- Light RW. Useful tests on the pleural fluid in the management of patients with pleural effusions. *Curr Opin Pulm Med* 1999;5:245-249.
- Long R, Nijoo H, Hershfield E. Tuberculosis: epidemiology of the disease in Canada. *CMAJ* 1999;160:1185-1190.
- Loughheed MD, Lemière C, Ducharme FM, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can Respir J* 2012;19:127-164.
- Mansharamani NG, Koziel H. Chronic lung sepsis: lung abscess, bronchiectasis, and empyema. *Cur Opin Pulmon Med* 2003;9:181-185.
- McLoud TJ, Swenson SJ. Lung carcinoma. *Clin Chest Med* 1999;20:697-713.
- McPhee SJ, Papadakis MA, Tierney LM. *Current medical diagnosis and treatment* 2007, 47th ed. USA: McGraw-Hill Professional, 2006.
- National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *NEJM* 2011;365:395-409.
- Nguyen HB, Rivers EP, Abrahamian FM, et al. Severe sepsis and septic shock: review of the literature and emergency department management guidelines. *Ann Emerg Med* 2006;48:28-54.
- O'Donnell DE, Hernandez P, Kaplan A, et al. Canadian thoracic society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. *Can Respir J* 2008;15(Suppl A):1A-8A.
- Ost D, Fein A. Evaluation and management of the solitary pulmonary nodule. *Am J Respir Crit Care Med* 2000;162(3 Pt 1):782-787.
- Ost D, Fein AM, Feinsilver SH. The solitary pulmonary nodule. *NEJM* 2003;348:2535-4252.
- Palda VA, Van Spall GCG with Canadian Task Force on Preventative Health Care. Screening for lung cancer: updated recommendations from the Canadian Task Force on Preventative Health Care. August 2003.
- Paramothayan NS, Lasserson TJ, Jones P. Corticosteroids for pulmonary sarcoidosis. *Cochrane DB Syst Rev* 2005;2:CD001114.
- Parfrey H, Chilvers ER. Pleural disease – diagnosis and management. *Practitioner* 1999;243:412,415-421.
- Pauwels RA, Buist AS, Kakkar PM. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. *Am J Resp and Crit Care Med* 2001;163:1256-1276.
- Ram FSF, Picot J, Lightowler J, Wedzicha, JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane DB Syst Rev* 2004;3:CD004104.
- Reimer LG. Community-acquired bacterial pneumonias. *Semin Respir Infect* 2000;15:95-100.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *NEJM* 2001;345:1368-1413.
- Sabatine MS. *Pocket medicine: the Massachusetts general hospital handbook of internal medicine*. Philadelphia: Lippincott Williams and Wilkins, 2004. p6-1 and 5-2.
- Scharschmidt, Bruce F. *Pocket medicine: internal medicine pulmonary medicine*. 2002. PocketMedicine.com.
- Schidlow DV, Taussig LM, Knowles MR. Cystic fibrosis foundation consensus conference report on pulmonary complications of cystic fibrosis. *Peds Pulmonol* 1993;15:187-196.
- Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *NEJM* 2013;368:709-718.
- Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54(1 Suppl):S43-54.
- Stein PD, Saltzman HA, Weg JG. Clinical characteristics of patients with acute pulmonary embolism. *Am J Cardiol* 1991;68:1723-1724.
- Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *NEJM* 2006;354:2317-2327.
- Tarascon Inc. *Tarascon Pocket Pharmacopoeia™*. Lompoc: Tarascon Publishing, 2004.
- Thrombosis Interest Group of Canada. Clinical guides. 27 brief, evidence-based guides on thrombosis for general practitioners (downloadable to a pda). Available from: [www.tigc.org](http://www.tigc.org).
- van den Bergh G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *NEJM* 2001;345:1359-1367.
- Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane DB Syst Rev* 2009;1:CD001288.
- Watts K, Chavasse RJ. Leukotriene receptor antagonists in addition to usual care for acute asthma in adults and children. *Cochrane DB Syst Rev* 2012;5:CD006100.
- Wongsurakiat P, Maranetra KN, Wasi C, et al. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest* 2004;125:2011-2020.

Faranak Esmaeilbeigi, Richard Norman and Alex Zhao, chapter editors

Grace Lam and Hamed Nazzari, associate editors

Gautam Goel, EBM editor

Dr. Lori Albert and Dr. Heather McDonald-Blumer, staff editors

<b>Anatomy of Joint Pathology</b> . . . . .	<b>2</b>	<b>SERONEGATIVE RHEUMATIC DISEASE</b>	
<b>Basics of Immunology</b> . . . . .	<b>2</b>	<b>Spondyloarthropathies</b> . . . . .	<b>21</b>
Immune Mechanisms of Disease		Ankylosing Spondylitis (AS)	
Immunogenetics and Disease		Enteropathic Arthritis (EA)	
<b>Differential Diagnoses of Common Presentations</b> . . . . .	<b>3</b>	Psoriatic Arthritis (PsA)	
<b>Synovial Fluid Analysis</b> . . . . .	<b>4</b>	Reactive Arthritis (ReA)	
<b>Septic Arthritis</b> . . . . .	<b>5</b>	<b>Crystal-Induced Arthropathies</b> . . . . .	<b>24</b>
<b>Degenerative Arthritis: Osteoarthritis (OA)</b> . . . . .	<b>5</b>	Gout	
<b>SEROPOSITIVE RHEUMATIC DISEASE Investigations</b> . . . . .	<b>6</b>	Pseudogout (Calcium Pyrophosphate Dihydrate Disease)	
<b>Connective Tissue Disorders</b> . . . . .	<b>8</b>	<b>Pediatric Rheumatology</b> . . . . .	<b>P96</b>
Rheumatoid Arthritis (RA)		<b>Non-Articular Rheumatism</b> . . . . .	<b>26</b>
Systemic Lupus Erythematosus (SLE)		Polymyalgia Rheumatica (PMR)	
Anti-phospholipid Antibody Syndrome (APLA)		Fibromyalgia	
Scleroderma		Adult Onset Still's Disease	
Idiopathic Inflammatory Myopathy		<b>Common Medications</b> . . . . .	<b>29</b>
Sjögren's Syndrome (SS)		<b>Landmark Rheumatology Trials</b> . . . . .	<b>31</b>
Mixed Connective Tissue Disease (MCTD)/Overlap Syndrome		<b>References</b> . . . . .	<b>32</b>
<b>Vasculitides</b> . . . . .	<b>17</b>		
Small Vessel Non-ANCA Associated Vasculitis			
Small Vessel ANCA-Associated Vasculitis			
Medium Vessel Vasculitis			
Large Vessel Vasculitis			

## Acronyms

Ab	antibody	GC	<i>Neisseria gonorrhea</i> /gonococcus	PMR	polymyalgia rheumatica
Ag	antigen	GCA	giant cell arteritis	PsA	psoriatic arthritis
ANA	antinuclear antibody	H/A	headache	PTT	partial thromboplastin time
Anti-Sm	anti-Smith antibodies	HA	hyaluronic acid	RA	rheumatoid arthritis
APLA	antiphospholipid antibody syndrome	Hb	hemoglobin	RBC	red blood cell
AS	ankylosing spondylitis	HLA	human leukocyte antigen	ReA	reactive arthritis
BUN	blood urea nitrogen	IA	intra-articular	RF	rheumatoid factor
CBC	complete blood count	IBD	inflammatory bowel disease	ROM	range of motion
CCP	cyclic citrullinated peptide	IE	infective endocarditis	SLE	systemic lupus erythematosus
CNS	central nervous system	MCP	metacarpal phalangeal joint	SS	Sjögren's syndrome
CRP	C-reactive protein	MCTD	mixed connective tissue disease	ULN	upper limit of normal
DIP	distal interphalangeal joint	MHC	major histocompatibility complex	VDRL	venereal disease research laboratory
EA	enteropathic arthritis	OA	osteoarthritis	WBC	white blood cell
ESR	erythrocyte sedimentation rate	PIP	proximal interphalangeal joint		

## Anatomy of Joint Pathology

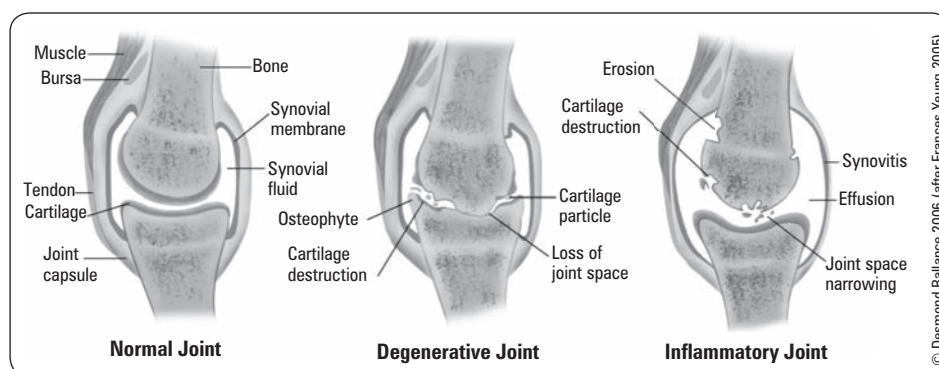


Figure 1. Structure of normal, degenerative and inflammatory joint



### Terminology in Rheumatology

#### Arthritis:

- Joint swelling: effusion/synovial thickening
- Decreased range of motion
- Stress pain
- Increased warmth

**Arthralgia:** perception of joint pain without obvious clinical findings

**Active joint:** swollen joint, joint line tenderness, or stress pain (pain at end of range of motion)

## Basics of Immunology

### Immune Mechanisms of Disease

Table 1. Mechanisms of Immunologically Mediated Disorders

Type	Pathophysiology	Examples
Anaphylactic (type I)	Formation of IgE → release of immunologic mediators from basophils/mast cells → diffuse inflammation	Asthma Allergic rhinitis
Cytotoxic (type II)	Formation of antibody (Ab) → deposit and bind to antigen (Ag) on cell surface → phagocytosis or lysis of target cell	Autoimmune hemolytic anemia, Goodpasture's syndrome, Graves' disease, pernicious anemia
Immune complex (type III)	formation of Ag-Ab complexes → activate complement → attract inflammatory cells and release of cytokines	SLE, PAN, post-streptococcal glomerulonephritis, serum sickness
Cell-mediated/delayed hypersensitivity (type IV)	Release of cytokines by sensitized T-cells and T-cell mediated cytotoxicity	Contact dermatitis

### Immunogenetics and Disease

- cell surface molecules called human leukocyte antigen (HLA) play a role in mediating immune reactions
- major histocompatibility complex (MHC) are genes on the short arm of chromosome 6 that encode HLA molecules
- there are three classes of MHC (see Table 2)
- discrete domains of hypervariability within MHC molecules thought to represent “susceptibility determinants”
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases (see Table 3)

Table 2. Classes of Major Histocompatibility Complexes (MHCs)

MHC Class	Types	Location	Function
I	HLA-A, B, C	All cells	Recognized by CD8+ (cytotoxic) T-lymphocytes
II	HLA-DP, DQ, DR	Antigen presenting cells (mononuclear phagocytes, B cells, others)	Recognized by CD4+ (helper) T-lymphocytes
III	Some components of the complement cascade	In plasma	Chemotaxis, opsonization, lysis of bacteria and cells

Table 3. HLA-Associated Rheumatic Disease

HLA Type	Associated Conditions	Comments
<b>B27</b>	Ankylosing spondylitis (AS) Reactive arthritis (ReA) Enteropathic arthritis (EA)	In AS, relative risk = 70-90 times In ReA, relative risk = 40 times
<b>DR4, DR1</b>	Rheumatoid arthritis (RA)	In RA, relative risk = 2-10 times; found in 93% of patients
<b>DR3</b>	Sjögren's syndrome SLE	DR3 associated with many non-rheumatic conditions (celiac disease, Type 1 DM, Graves' disease, chronic active hepatitis)

## Differential Diagnoses of Common Presentations

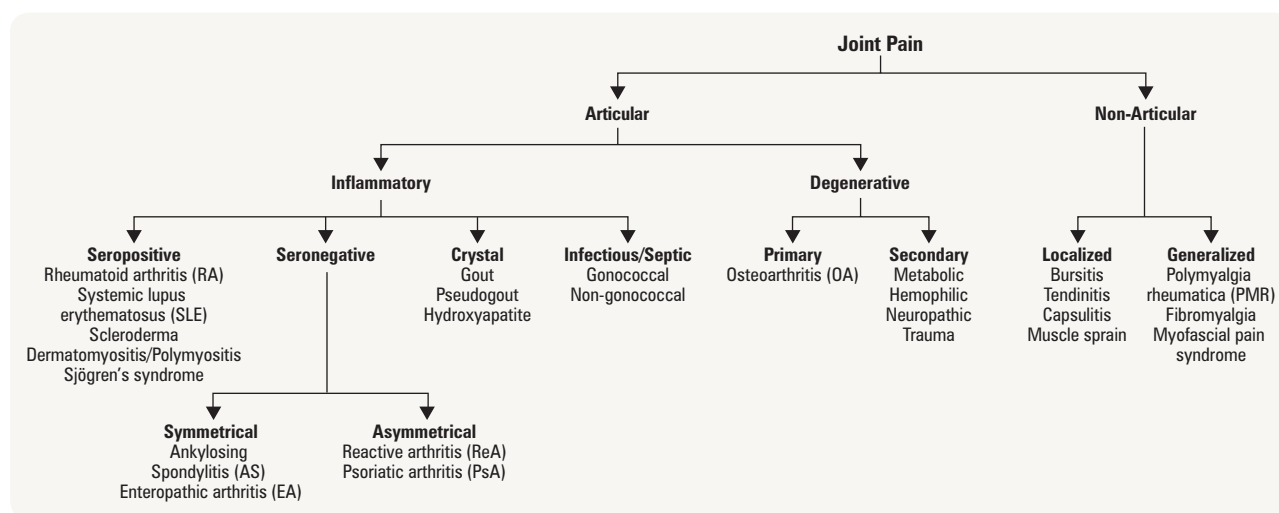


Figure 2. Clinical approach to joint pain

Table 4. Differential Diagnosis of Monoarthritis

Infection	Crystal	Degenerative	Trauma	Neoplastic	Other
Septic arthritis (staph, gonococcal, fungi, TB)	Gout Pseudogout Hydroxyapatite	Osteoarthritis	Hemarthrosis Osteonecrosis	Tumour	Systemic inflammatory disease Polyarthritis presenting with monoarticular symptoms first

Table 5. Differential Diagnosis of Oligoarthritis/Polyarthritis

Acute (<6 weeks)	Chronic (>6 weeks)		
First presentation of inflammatory arthritis Post-viral (parvovirus B19) Acute rheumatic fever Infectious (GC, non-GC)	<b>Seropositive inflammatory arthritis</b> Rheumatoid arthritis Systemic lupus erythematosus Scleroderma Polymyositis/dermatomyositis	<b>Seronegative inflammatory arthritis</b> Ankylosing spondylitis Enteropathic arthritis Psoriatic arthritis Reactive arthritis Crystal (polyarticular gout)	<b>Degenerative</b> Osteoarthritis

Table 6. Symptoms of Inflammatory Arthritis vs. Degenerative Arthritis

Inflammatory	Degenerative
Pain at rest, relieved by motion Morning stiffness >1 h Warmth, swelling, erythema Malalignment/deformity Extra-articular manifestations	Pain with motion, relieved by rest Morning stiffness <½ h Joint instability, buckling, locking Bony enlargement, malalignment/deformity



### Causes of Joint Pain

#### SOFTER TISSUE

Sepsis  
OA  
Fracture  
Tendon/muscle  
Epiphyseal  
Referred  
Tumour  
Ischemia  
Seropositive arthritides  
Seronegative arthritides  
Urate (gout)/other crystal  
Extra-articular rheumatism (PMR/fibromyalgia)



### Patterns of Joint Involvement

- Symmetrical vs. asymmetrical
- Small vs. large
- Mono vs. oligo (2-4 joints) vs. polyarticular (≥5 joints)
- Axial vs. peripheral

Table 7. Seropositive vs. Seronegative Rheumatic Diseases

	Seropositive	Seronegative
<b>Demographics</b>	F > M	M > F
<b>Peripheral Arthritis</b>	Symmetrical Small (PIP, MCP) and medium joints (wrist, knee, ankle, elbow) common DIP less involved	Usually asymmetrical Usually larger joints, lower extremities (psoriatic arthritis may be the exception) DIP in psoriatic arthritis Dactylitis ("sausage digit") Enthesitis
<b>Pelvic/Axial Disease</b>	No (except for C-spine)	Yes
<b>Enthesitis</b>	No	Yes
<b>Extra-Articular</b>	Nodules Vasculitis Sicca Raynaud's phenomenon	Iritis (= anterior uveitis) Oral ulcers GI Dermatologic features

### Common Investigations in Rheumatology

- general: CBC, electrolytes, Cr
- acute phase reactants: ESR, CRP, ferritin, albumin, fibrinogen
- complement (C3, C4)
- urinalysis to detect disease complications (proteinuria, active sediment)
- serology: autoimmune Abs (ANA, anti-dsDNA, anti-Jo-1, anti-Sm, anti-La, anti-Ro, RhF, and anti-CCP, etc.)
- synovial fluid analysis
- radiology (plain film, CT, MRI, U/S, bone densitometry, angiography, bone scan)

## Synovial Fluid Analysis

- synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage

### Indications

- diagnostic: mandatory if septic arthritis suspected; advised if crystal arthritis or hemarthrosis suspected; advised if unexplained effusion in accessible joint
- therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection

### Contraindications

- absolute: open lesion or suspected infection of overlying skin or soft tissue
- relative: bleeding diathesis, thrombocytopenia, prosthetic joint

### Most Important Tests of Synovial Fluid (3 Cs)

- ensure synovial fluid is described in terms of colour, clarity, viscosity, and quantity
- 1. Cell count and differential
- 2. Culture and Gram stain (bacteria, mycobacteria, fungi)
- 3. Crystal examination (microscopy with polarized light)
  - gout (monosodium urate) → needle-shaped, negatively birefringent (bright yellow)
  - pseudogout (calcium pyrophosphate dihydrate) → rhomboid-shaped, positively birefringent (pale blue)



Protein, LDH, glucose less helpful.

Table 8. Synovial Fluid Analysis

Parameter	Normal	Non-Inflammatory	Inflammatory	Infectious	Hemorrhagic
<b>Colour</b>	Pale yellow	Pale yellow	Pale yellow	Yellow to white	Red/brown
<b>Clarity</b>	Clear	Clear	Opaque	Opaque	Sanguinous
<b>Viscosity</b>	High (due to hyaluronic acid)	High	Low	Low or paradoxically high if purulent	Variable
<b>WBC/mm<sup>3</sup></b>	<200	<2000	>2000	Higher cell counts (particularly >50,000) suggestive	Variable
<b>% PMN</b>	<25%	<25%	>25%	>75%	Variable
<b>Culture/ Gram stain</b>	–	–	–	Usually positive	–
<b>Examples</b>		Trauma Osteoarthritis Neuropathy Hypertrophic – arthropathy	Seropositives Seronegatives Crystal arthropathies	<i>S. aureus</i> Gram negative Gonococcal → difficult to culture	Trauma Hemophilia

## Septic Arthritis

- for any acute monoarticular arthritis, one must rule out septic etiology; consider empiric antibiotic treatment until septic arthritis is excluded by history, physical exam and synovial fluid analysis
- poor prognostic factors : older age, immunocompromised, delay in treatment, previously damaged joint, joint prosthesis
- see [Infectious Diseases](#) for *Gonococcal Arthritis*, ID15/[Orthopedics](#), OR10



Septic arthritis is a medical emergency!



## Degenerative Arthritis: Osteoarthritis (OA)

### Definition

- progressive deterioration of cartilage and bone due to failed repair of joint damage caused by stresses on the joint

### Classification (based on etiology)

- primary (idiopathic)
  - most common, unknown etiology
- secondary
  - post-traumatic or mechanical
  - post-inflammatory (e.g. RA) or post-infectious
  - heritable skeletal disorders (e.g. scoliosis)
  - endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
  - metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
  - neuropathic (e.g. Charcot joints)
    - ♦ atypical joint trauma due to peripheral neuropathy (e.g. diabetes, syphilis)
  - avascular necrosis
  - other (e.g. congenital malformation)

### Pathophysiology

- deterioration of articular cartilage due to local biomechanical factors and release of proteolytic and collagenolytic enzymes
  - OA develops when cartilage catabolism > synthesis
  - loss of proteoglycans and water exposes underlying bone
- abnormal local bone metabolism further damages joint
- altered joint function and damage
- synovitis is secondary to cartilage damage; therefore, may see small effusions in OA

### Epidemiology

- most common arthropathy
- increased prevalence with increasing age (35% of 30 yr olds, 85% of 80 yr olds)

### Risk Factors

- genetic predisposition, advanced age, obesity (for knee OA), female, trauma

### Signs and Symptoms

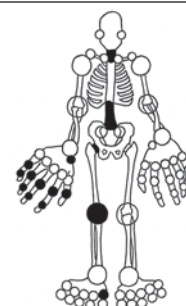
- localized to affected joints (not a systemic disease)
- pain is often insidious, gradually progressive, with intermittent flares and remissions

Table 9. Signs and Symptoms of OA

Signs	Symptoms
Joint line tenderness; stress pain $\pm$ joint effusion	Joint pain with motion; relieved with rest
Bony enlargement at affected joints	Short duration of stiffness (<1/2 h) after immobility
Malalignment/deformity (angulation)	Joint instability/buckling
Limited ROM	Joint locking due to "joint mouse" (bone or cartilage fragment)
Crepitus on passive ROM	Loss of function or other internal derangements (e.g. meniscal tear)
Inflammation (mild if present)	
Periarticular muscle atrophy	

### Joint Involvement (see Figure 3)

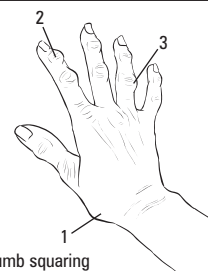
- asymmetric
- hand (see Figure 4)
  - DIP (Heberden's nodes = osteophytes  $\rightarrow$  enlargement of joints)
  - PIP (Bouchard's nodes)
  - CMC (usually thumb squaring)
  - 1<sup>st</sup> MCP (other MCPs are usually spared)



- Hand (DIP, PIP, 1st CMC)
- Hip
- Knee
- 1st MTP
- L-spine (L4-L5, L5-S1)
- C-spine
- Uncommon: ankle, shoulder, elbow, MCP, rest of wrist

© Linda Colati

Figure 3. Common sites of involvement in OA



1. Thumb squaring
2. Heberden's nodes
3. Bouchard's nodes

© Tabby Lulham 2011

Figure 4. Hand findings in OA



OA of MCP joints can be seen in hemochromatosis or chondrocalcinosis.



- hip
  - usually presents as groin pain  $\pm$  dull or sharp pain in the trochanteric area, internal rotation and abduction are lost first
  - pain can radiate to the anterior thigh but generally does not go below the knee
- knee
  - initial narrowing of one compartment, medial > lateral; seen on standing x-rays, often patellar-femoral joint involved
- foot
  - common in first MTP and midfoot
- lumbar spine
  - very common, especially L4-L5, L5-S1
  - degeneration of intervertebral discs and facet joints
  - reactive bone growth can contribute to neurological impingement (e.g. sciatica, neurogenic claudication) or spondylolisthesis (forward or backward movement of one vertebra over another)
- cervical spine
  - commonly presents with neck pain and to scapula, especially in mid-lower cervical area (C5 and C6)

### Investigations

- blood work
  - normal CBC and ESR, CRP
  - negative RF and ANA
- radiology: 4 hallmark findings (see sidebar)
- synovial fluid: non-inflammatory (see Table 8)

### Treatment

- presently no treatment alters the natural history of OA
- **non-pharmacological therapy**
  - weight loss (minimum 5-10 lb loss) if overweight
  - physiotherapy: heat/cold, low impact exercise programs
  - occupational therapy: aids, splints, cane, walker, bracing
- **pharmacological therapy** (see Table 31)
  - oral: acetaminophen/NSAIDs, glucosamine  $\pm$  chondroitin (nutraceuticals not proven)
  - joint injections: corticosteroid, hyaluronic acid (questionable benefit)
  - topical: capsaicin, NSAIDs
- **surgical treatment**
  - joint debridement, osteotomy, total and/or partial joint replacement, fusion (see [Orthopedics](#), OR10)



**Hint:** Bouchard's is closer to the Body



### The Radiographic Hallmarks of OA

- Joint space narrowing
- Subchondral sclerosis
- Subchondral cysts
- Osteophytes



### Meta-analysis: Chondroitin for Osteoarthritis of the Knee and Hip

*Ann Intern Med* 2007;146:580-590

**Study:** Meta-analysis of 20 RCTs and quasi-RCTs (n=3846) examining the efficacy of chondroitin on OA.

**Results:** The analysis of this review was hampered by significant trial heterogeneity. Trials with poor methodology (small numbers, inadequate randomization concealment, no intention to treat analysis) showed larger effect sizes in favour of chondroitin. When the authors restricted analysis to 3 trials with large sample sizes and an ITT analysis, 40% of patients were included and an effect size of -0.03 (95% CI -0.13 to 0.07) was generated.

**Conclusion:** There is high quality evidence to suggest there is no difference between chondroitin and placebo. Chondroitin should be discouraged from routine use in clinical practice.



### Intraarticular Corticosteroid for Treatment of Osteoarthritis of the Knee

*Cochrane DB Syst Rev* 2009;CD005328

**Population:** Patients with osteoarthritis (OA) of the knee.

**Intervention:** Intraarticular (IA) corticosteroid injection.

**Results:** 28 RCTs and quasi-RCTs (n=1973). IA corticosteroids were more effective than placebo for pain reduction and global assessment at one wk post-injection. There was significant pain reduction at 2 and 3 wk, but no benefit for pain and function beyond 4 wk post-injection. There was no benefit for global function beyond 1 wk post-injection. There were higher rates of pain reduction at 4 wk post-injection for triamcinolone hexacetonide versus betamethasone. There was no difference between IA corticosteroids and joint lavage in outcomes or safety. Hyaluronic acid (HA) injections showed better response than IA corticosteroids between 5 and 13 wk post-injection.

**Conclusion:** IA corticosteroid injection is effective for the short-term treatment of OA of the knee with few side effects. HA therapy can provide more durable results.



### Glucosamine Therapy for Treating Osteoarthritis

*Cochrane DB Syst Rev* 2009;CD002946

**Study:** Meta-analysis of 25 RCTs (n=4963) examining the efficacy of glucosamine on OA.

**Results:** Collectively the 25 RCTs favoured glucosamine over placebo for total reduction in pain with 22% improvement as well as improvement in function using the Lequesne index. However, results were not uniformly positive. Only the glucosamine containing Rotta preparation was found to be significant. Rotta preparation also showed that glucosamine was able to slow radiological evidence of OA over a 3 yr period.

Glucosamine had an excellent safety profile.

**Conclusion:** Rotta preparation of glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from OA.

## SEROPOSITIVE RHEUMATIC DISEASE

- seropositive arthropathies are characterized by the presence of a serologic marker such as a positive rheumatoid factor or ANA
- the vasculitides are not seropositive diseases – some may be ANCA positive

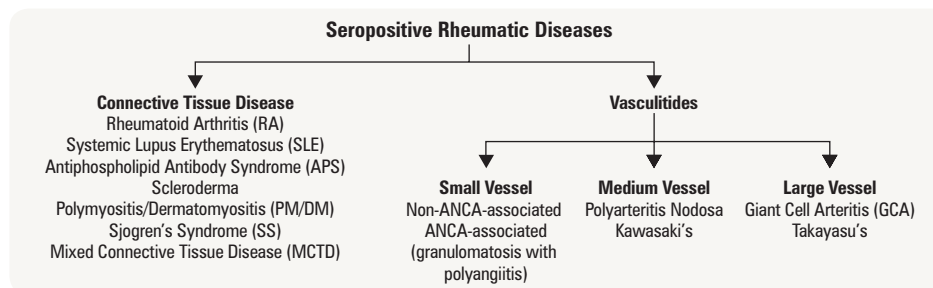


Figure 5. Seropositive rheumatic diseases

## Investigations

### Bloodwork

- general: CBC, creatinine
- acute phase reactants: ESR, CRP, ferritin, albumin, complement (C3 and C4), fibrinogen,
- Note: C3, C4 often decrease in active SLE
- autoantibodies (see Table 10)

### Urinalysis

- proteinuria, active sediment
- synovial fluid analysis (see Table 8)
- radiology (plain film, CT, MRI, ultrasound, bone densitometry, angiography, bone scan)



#### Differential Diagnosis of Elevated ESR

- RA, PMR, GCA
- Hypoalbuminemia, anemia, multiple myeloma
- Bacterial infections
- Malignancy

ESR (and CRP) is insensitive for PM/DM, AS, scleroderma, SLE, viral infections

**Table 10. Autoantibodies and their Prevalence in Rheumatic Diseases**

Autoantibody	Disease	Normal	Comments
<b>RF</b>	RA 80%	<5%	Autoantibodies (IgM>IgG>IgA) directed against Fc domain of IgG Present in most seropositive diseases Levels correlate with disease severity in RA Non-specific; may be present in IE, TB, hepatitis C, silicosis, sarcoidosis
	SS 50%	10-20%	
	SLE 20%	>65	
<b>Anti-CCP</b>	RA 80%		In RA: anti CCP more specific than RF May be useful in early disease and to predict aggressive disease
<b>ANA</b>	SLE 98%	<5% (seen in other CTDs)	Antibodies against nuclear components (DNA, RNA, histones, centromere) 1:40 dilution found in 5-30% of the normal population Sensitive but not specific for SLE
	MCTD 95%		
	SS 70-90%		
	CREST 80%		
<b>Anti-dsDNA</b>	SLE 50-70%	0%	Specific for SLE Levels correlate with disease activity
<b>Anti-Sm</b>	SLE <30%	0%	Specific but not sensitive for SLE
<b>Anti-Ro (SSA)</b>	SS 40-95%	0.5%	Subacute cutaneous SLE and mothers of babies with neonatal SLE 25%
<b>Anti-La (SSB)</b>	SS 40% SLE 10%	0%	Usually occurs with anti-Ro
<b>Antiphospholipid antibodies (LAC, ACLA)</b>	APS 100% SLE 31-40%	<5%	By definition present in APS Only small subset of SLE patients develop clinical syndrome of APS If positive will often get a false positive VDRL test
<b>Anti-histone</b>	Drug-induced SLE >90%	0%	
	Idiopathic SLE >50%	0%	
<b>Anti-RNP</b>	MCTD		Present in MCTD; present in many other CTD
<b>Anti-centromere</b>	CREST >80%	0%	Specific for CREST variant of systemic sclerosis
<b>Anti-topoisomerase I (formerly Scl-70)</b>	Diffuse systemic sclerosis 26-76%	0%	
<b>c-ANCA</b>	Active GPA (granulomatosis with polyangiitis) >90%	0%	Specific and sensitive
<b>p-ANCA</b>	GPA (granulomatosis with polyangiitis) 10% Other vasculitis	0%	Nonspecific and poor sensitivity (found in ulcerative colitis, polyarteritis nodosa, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis)
<b>Anti-Mi-2</b>	DM 15-20%		Specific but not sensitive (not available in all centres)
<b>Antibodies against RBCs, WBCs, or platelets</b>	SLE		Perform direct Coomb's test Test hemoglobin, reticulocyte, leukocyte and platelet count, antiplatelet Abs

- note: some individuals in the normal population test positive for RF and/or ANA, but do not have the conditions listed

## Connective Tissue Disorders

**Table 11. Features of Seropositive Arthropathies**

	RA	SLE	Scleroderma	Dermatomyositis
<b>CLINICAL FEATURES</b>				
<b>History</b>	Symmetrical polyarthritis (small joint involvement) AM stiffness (>1 h)	Multisystemic disease: rash, photosensitivity, Raynaud's, alopecia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis	Skin tightness, stiffness of fingers, Raynaud's, heartburn, dysphagia, pulmonary hypertension, renal dysfunction, dyspnea on exertion	Heliotrope rash (periocular), Gottron's papules (violaceous papules over knuckles and IP joints) ± poikiloderma Shawl sign macular erythema over chest and shoulder Proximal muscle weakness ± pain Dyspnea on exertion
<b>Physical Examination</b>	Effused joints Tenosynovitis Nodules Joint deformities Bone-on-bone crepitus	Confirm historical findings (rash, serositis, renal, CVS, etc.) ± effused (typically small) joints (can be minimal, look for soft tissue swelling)	Skin tightness on dorsum of hand, facial skin tightening, telangiectasia, calcinosis, non-effused joint, inspiratory crackles	Rash, proximal muscle weakness, inspiratory crackles
<b>LABORATORY</b>				
<b>Non-specific</b>	↑ ESR in 50-60% ↑ platelets ↓ Hb ↓ WBC (Felty's)	↑ ESR ↓ platelets (autoimmune) ↓ Hb (autoimmune) ↓ WBC (leukopenia, lymphopenia)	↑ ESR ↓ Hb Normal WBC	Possible increased ESR ↓ Hb Normal WBC
<b>Specific</b>	RF +ve in ~80% Anti-CCP +ve in ~80%	ANA +ve in 98% Anti-dsDNA +ve in 50-70% Anti-SM +ve in 30% ↓ C3, C4, total hemolytic complement False positive VDRL (in lupus subtypes) ↑ PTT (in lupus subtypes; e.g. anti-phospholipid Ab)	ANA +ve in >90% Anti-topoisomerase 1 (diffuse) Anti-centromere (usually in CREST, see RH13)	CK elevated in 80% ANA +ve in 33% anti-Jo-1, anti-Mi-2 Muscle biopsy EMG MRI
<b>Synovial Fluid</b>	Inflammation Leukocytosis (>10,000)	Mild inflammation with +ve ANA	Not specific	Not specific
<b>Radiographs</b>	Periarticular osteopenia Joint space narrowing Erosions Absence of bone repair Symmetric/concentric	Non-erosive ± osteopenia ± soft tissue swelling	± pulmonary fibrosis ± esophageal dysmotility ± calcinosis ± interstitial lung disease	± esophageal dysmotility ± interstitial lung disease ± calcifications

## Rheumatoid Arthritis (RA)

### Definition

- chronic, symmetric, erosive synovitis of peripheral joints (i.e. wrists, MCPs, MTPs)
- characterized by a number of extra-articular features

**Table 12. Classification Criteria for RA**

Criteria	Score	Comments
1. Joint involvement (swollen or tender)		
1 large joint (shoulders, elbows, hips, knees, and ankles)	0	
2-10 large joints	1	
1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs)	2	
4-10 small joints	3	
>10 joints (at least 1 small joint)	5	
2. Serology		Total score of ≥6: definite RA Must have at least ≥1 joint with definite clinical swelling, not better explained by other disease
Negative RF and negative Anti-CCP	0	
Low-positive RF or low-positive Anti-CCP (<3x ULN)	2	
High-positive RF or high-positive Anti-CCP (>3x ULN)	3	
3. Acute phase reactants		
Normal CRP and normal ESR	0	
Abnormal CRP and abnormal ESR	1	
4. Duration of symptoms		
<6 wk	0	
≥6 wk	1	

See sidebar for 1987 criteria. Reference: Arthritis Rheum 2010;62:2569-2581



RA is an independent risk factor for atherosclerosis and CV disease  
RA is associated with increased overall mortality/morbidity from all causes:  
CV disease, neoplasm (especially lymphoma), infection.



### Common Presentation

- Morning stiffness >1 h, improves with use
- Symmetric joint involvement
- Initially involves small joints of hands and feet
- Constitutional symptoms



### 1987 American Rheumatism Association RA criteria

At least 4 of:

- Morning stiffness >1 h for >6 wk
- Arthritis ≥3 joints for >6 wk
- Arthritis of hand joints for >6 wk
- Symmetric arthritis for >6 wk
- Rheumatoid nodules
- Serum RF positive
- Radiographic changes (erosions or periarticular osteopenia)

Criteria are 91-94% sensitive and 89% specific for RA.

### Pathophysiology

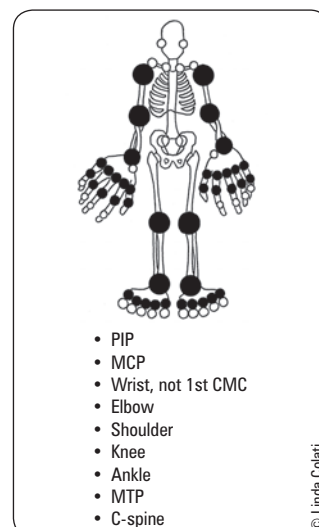
- autoimmune disorder, unknown etiology
- hallmark of RA is hypertrophy of the synovial membrane
  - activated rheumatoid synovium (pannus) grows into and over the articular surface; inflammatory mediators lead to release of metalloproteinases and collagenases resulting in destruction of articular cartilage and subchondral bone
- two theories attempt to explain chronic remissions and exacerbations seen in RA
  - **sequestered Ag**
    - ♦ during inflammation, immune complexes (ICs) are deposited at avascular cartilage-bone junction → ICs are released as further cartilage breaks down → triggers inflammatory cascade
  - **molecular mimicry**
    - ♦ cartilage damage → altered cartilage resembles undefined offending agent → triggers inflammatory cascade

### Epidemiology

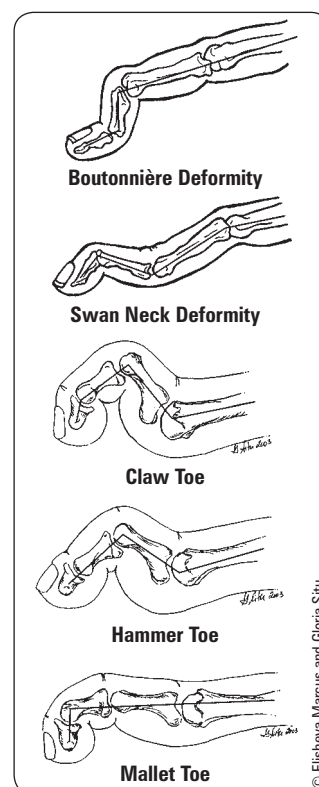
- prevalence 1% of adult population
- F:M = 3:1
- age of onset 20-40 yr
- genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type)

### Signs and Symptoms

- variable course of exacerbations and remissions
- morning stiffness >1 h, improves with use, increases with rest
- may have joint pain with activity
- symmetric joint involvement (see Figure 6)
- joint swelling, tender joints
- signs of mechanical joint damage: loss of motion, instability, deformity, crepitus
- constitutional symptoms: profound fatigue; rarely myalgia or weight loss
- extra-articular features (EAF) (see Table 13)
- limitation of function and decrease in global functional status
- complications of chronic synovitis
  - signs of mechanical joint damage: loss of motion, instability, deformity, crepitus
  - joint deformities (see Figure 7)
    - ♦ swan neck deformity, boutonnière deformity
    - ♦ ulnar deviation of MCP, radial deviation of wrist joint
    - ♦ hammer toe, mallet toe, claw toe
    - ♦ flexion contractures
  - atlanto-axial and subaxial subluxation
    - ♦ C-spine instability
    - ♦ neurological impingement (long tract signs)
    - ♦ difficult/dangerous intubation: risk of worsening subluxation and damage to spinal cord
  - limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
  - tenosynovitis → may cause rupture of tendons
  - carpal tunnel syndrome
  - ruptured Baker's cyst (outpouching of synovium behind the knee); presentation similar to acute DVT



**Figure 6. Common sites of joint involvement in RA**



**Figure 7. Joint deformities**

**Table 13. Extra-Articular Features of RA Classified by Underlying Pathophysiology**

System	Vasculitic	Lymphocytic Infiltrate
<b>Skin</b>	Periungual infarction, cutaneous ulcers, palpable purpura	Rheumatoid nodules (may have vasculitic component)
<b>Ocular</b>	Episcleritis, scleritis	Keratoconjunctivitis sicca (see sidebar)
<b>Head and Neck</b>		Xerostomia (see sidebar), Hashimoto's thyroiditis (see <a href="#">Endocrinology, E27</a> )
<b>Cardiac</b>		Peri-/myocarditis, valvular disease, conduction defects
<b>Pulmonary</b>		Pulmonary fibrosis, pleural effusion, pleuritis, pulmonary nodules
<b>Neurologic</b>	Peripheral neuropathy: sensory stocking-glove, mononeuritis multiplex	
<b>Hematologic</b>		Splenomegaly, neutropenia (Felty's, see sidebar)
<b>Renal</b>		Amyloidosis – caused by accumulation of abnormal proteins

### Classification of Global Functional Status in RA (American College of Rheumatology, 1991)

- **Class I:** able to perform usual ADLs (self-care, vocational, avocational)
- **Class II:** able to perform self-care and vocational activities, restriction of avocational activities
- **Class III:** able to perform self-care, restriction of vocational and avocational activities
- **Class IV:** limited ability to perform self-care, vocational, avocational activities



#### Syndromes in RA

- Sjögren's syndrome (common): keratoconjunctivitis sicca and xerostomia (dry eyes and mouth)
- Caplan's syndrome (rare): multiple pulmonary nodules and pneumoconiosis
- Felty's syndrome (rare): arthritis, splenomegaly, neutropenia

## Investigations

- bloodwork
  - RF sensitivity ~80% but non-specific (see Table 10); may not be present at onset of symptoms
  - anti-CCP (cyclic citrullinated peptide): sensitivity ~80% but more specific; may precede onset of symptoms
  - increased disease activity is associated with decreased Hb (anemia of chronic disease), increased platelets, ESR, CRP, and RF
- imaging
  - x-rays may be entirely normal at onset
  - first change is periarticular osteopenia, followed by erosions
  - ultrasound, MRI may be used to image hands to detect early synovitis and erosions

## Treatment

- goals of therapy: remission or lowest possible disease activity
  - control disease activity
  - relieve pain and stiffness
  - maintain function and lifestyle
  - prevent or control joint damage
  - key is early diagnosis and early intervention with disease-modifying anti-rheumatic drugs (DMARDs)
  - “window of opportunity” = early treatment within first 3 mo of disease may allow better control/remission

## Education

- The Arthritis Society (Canada) and Arthritis Foundation (U.S.) for educational resources

## Behavioral

- exercise program (isometrics and active, gentle ROM exercise during flares, aquatic/aerobic/strengthening exercise between flares), assistive devices as needed
- job modification may be necessary

## Pharmacologic

### 1. Disease Modifying Anti-Rheumatic Drugs (DMARDs) and Biologics (see Table 32)

- **DMARDs:** standard of care and should be started as soon as possible
- treatments guided by disease severity and prognostic features
- methotrexate is the gold standard and is first-line unless contraindicated
- delayed onset of action (may take 8-12 wk)
- potential toxicities: GI, hematologic, hepatic (liver enzymes), pulmonary, teratogenic
- if inadequate response (3-6 mo) → combine or switch
- add-ons include: hydroxychloroquine, sulfasalazine, leflunomide
- **biologics:** indicated if inadequate response to DMARDs
  - ♦ can be combined with DMARD therapy
  - ♦ agents include abatacept, rituximab, tocilizumab
  - ♦ reassess every 3-6 mo and monitor disease severity

### 2. Reducing Inflammation and Pain

- NSAIDs
  - ♦ individualize according to efficacy and tolerability
  - ♦ contraindicated or cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy, see Table 31), add acetaminophen ± opioid prn for synergistic pain control
- corticosteroids
  - ♦ local
    - intra-articular injections to control symptoms in a specific joint
  - ♦ systemic (prednisone)
    - low dose (5-10 mg/d) useful for short term to improve symptoms if NSAIDs ineffective, to bridge gap until DMARD takes effect
    - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy if using corticosteroids >3 mo at >7.5 mg/d
    - cautions/contraindications: active infection, TB, osteoporosis, hypertension, gastric ulcer, diabetes

## Surgical Therapy

- indicated for structural joint damage
- surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair



Poor prognostic features of RA include: young age of onset, high RF titer, elevated ESR, activity of >20 joints, and presence of EAF.



### Side Effects of Steroids

- Weight gain
- Osteoporosis
- Avascular necrosis (AVN)
- Cataracts, glaucoma
- Peptic ulcer disease (PUD)
- Susceptibility to infection
- Easy bruising
- Acne
- Hypertension
- Hyperlipidemia
- Hypokalemia, hyperglycemia
- Mood swings



Only DMARDs (not analgesics or NSAIDs) alter the course of RA!



### Comparison of Treatment Strategies in Early Rheumatoid Arthritis

*Ann Intern Med* 2007;146:406-415

**Study:** RCT of 508 patients comparing 4 different treatment strategies for early rheumatoid arthritis (known as the BEST trial).

#### Intervention:

- Group 1: Sequential Monotherapy with traditional DMARDs
- Group 2: Step-Up Combination Therapy
- Group 3: Initial Combination Therapy with prednisone (high dose)
- Group 4: Initial Combination Therapy with infliximab

**Results:** Patients in groups 3 and 4 responded faster and had significantly greater overall change in physical function scores after the first year of treatment. By end of the second yr, groups 1 and 2 had achieved a similar response to groups 3 and 4. Groups 3 and 4 also showed significantly less radiologic progression of their disease over 2 yr than groups 1 and 2. There were no significant differences in toxicity levels between the 4 groups.

**Conclusions:** Initial combination therapy with prednisone or infliximab results in faster response rates. Whether faster initial response rates leads to better long-term disease outcomes has not yet been studied.



## Systemic Lupus Erythematosus (SLE)

- please see [Nephrology](#), NP24 and [Dermatology](#), D39 for additional details



### Definition

- chronic inflammatory multi-system disease of unknown etiology
- characterized by production of autoantibodies and diverse clinical manifestations

**Table 14. Diagnostic Criteria of SLE: 4 or more of 11 must be present serially or simultaneously**

Criteria	Description
<b>CLINICAL</b>	
Malar rash	Classic "butterfly rash", sparing of nasolabial folds, no scarring
Discoid rash	May cause scarring due to invasion of basement membrane
Photosensitivity	Skin rash in reaction to sunlight
Oral/nasal ulcers	Usually painless
Arthritis	Symmetric, involving $\geq 2$ small or large peripheral joints, non-erosive
Serositis	Pleuritis or pericarditis
Neurologic disorder	Seizures or psychosis
<b>LABORATORY</b>	
Renal disorder	Proteinuria ( $>0.5$ g/d or 3+) <ul style="list-style-type: none"> <li>Cellular casts (RBC, Hb, granular, tubular, mixed)</li> </ul>
Hematologic disorder	Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
Immunologic disorder	Anti-dsDNA or anti-Sm or antiphospholipid antibodies (anticardiolipin Ab, lupus anticoagulant) or false positive VDRL with 6 mo confirmation that it's negative
Antinuclear antibody (ANA)	Most sensitive test (98%), not specific

Note: "4, 7, 11" rule  $\rightarrow$  4 out of 11 criteria (4 lab, 7 clinical) for diagnosis  
American College of Rheumatology, 1997 update

### Etiology and Pathophysiology

- production of autoantibodies causing multi-organ inflammation
- multi-factorial etiology (see Figure 8)
- **genetics**
  - common association with HLA-B8/DR3;  $\sim 10\%$  have positive family history
- **estrogen**
  - pre-pubertal and post-menopausal women have similar incidence to men
  - men with SLE have higher concentration of estrogenic metabolites
- **infection**
  - viral (non-specific stimulant of immune response)
- **drug-induced**
  - anti-hypertensives (hydralazine), anti-convulsants (phenytoin), anti-arrhythmics (procainamide), isoniazid, biologics, oral contraceptive pills
  - anti-histone antibodies are commonly seen in drug-induced lupus
  - symptoms resolve with discontinuation of offending drug

### Epidemiology

- prevalence: 0.05% overall
- F:M = 10:1
- age of onset in reproductive yr (13-40)
- more common and severe in African-Americans and Asians
- bimodal mortality pattern
  - early (within 2 yr)
    - ♦ active SLE, active nephritis, infection secondary to steroid use
  - late ( $>10$  yr)
    - ♦ inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation

### Signs and Symptoms

- characterized by periods of exacerbation and remission



#### The Safety of Infliximab, Combined with Background Treatments, among Patients with Rheumatoid Arthritis and Various Comorbidities (START)

*Arthritis Rheum* 2006;54:1075-1086  
Study: Multicenter RCT.

**Patients:** 1084 patients (mean age 52 yr, 80% female) with active moderate to severe rheumatoid arthritis despite treatment with methotrexate.

**Intervention:** Patients were randomized to receive infusions of placebo, infliximab dosed at 3 mg/kg, or infliximab dosed at 10 mg/kg at 0, 2, 6, and 14 wk, in addition to methotrexate.

**Primary Outcome:** Incidence of serious infection within 22 wk.

**Results:** Compared with the placebo group, the relative risk of developing serious infection at 3 mg/kg and 10 mg/kg of infliximab was 1.0 (95% CI 0.3-3.1,  $p=0.995$ ) and 3.1 (95% CI 1.2-7.9,  $p=0.013$ ) respectively. In addition, 31% of patients receiving infliximab at 3 mg/kg and 32% of patients receiving infliximab at 10 mg/kg were able to achieve remission at 22 wk compared with only 14% of those receiving placebo ( $p<0.001$ , NNT=6).

**Conclusions:** Therapy with infliximab 3 mg/kg does not significantly increase the risk of serious infection in patients with active moderate to severe rheumatoid arthritis already receiving methotrexate. However, therapy with infliximab 10 mg/kg does significantly increase the risk of serious infection in this population.



#### Diagnostic Criteria of SLE

##### MD SOAP BRAIN

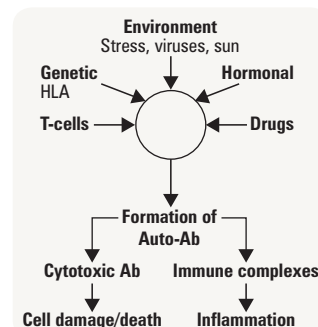
Malar rash	Blood
Discoid rash	Renal
Serositis	Arthritis
Oral ulcers	Immune
ANA	Neurologic
Photosensitivity	



Radiographically, the arthritis of SLE is non-erosive (unlike RA).



Consider SLE in a patient who has involvement of 2 or more organ systems.



**Figure 8. Multi-factorial etiology of SLE**



Table 15. Symptoms of SLE

System	Symptoms
<b>Systemic</b>	Fatigue, malaise, weight loss, fever, lymphadenopathy
<b>Renal</b>	Hypertension, peripheral edema, glomerulonephritis, renal failure
<b>Derm</b>	Photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura, panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria
<b>MSK</b>	Polyarthralgias, polyarthritis, myalgias, avascular necrosis. Reducible deformities of hand = Jaccoud's arthritis
<b>Ophthalmic</b>	Keratoconjunctivitis sicca, episcleritis, scleritis, cytooid bodies (cotton wool exudates on fundoscopy = infarction of nerve cell layer of retina)
<b>Cardiac</b>	Pericarditis, coronary artery disease, non-bacterial endocarditis (Libman-Sachs) Note: SLE is an independent risk factor for atherosclerosis and CV
<b>Vascular</b>	Raynaud's phenomenon, livedo reticularis (mottled discolouration of skin due to narrowing of blood vessels, characteristic lacy or net-like appearance), thrombosis, vasculitis
<b>Resp</b>	Pleuritis, interstitial lung disease, pulmonary hypertension, PE, alveolar hemorrhage
<b>GI</b>	Pancreatitis, lupus enteropathy, hepatitis, hepatomegaly
<b>Neurologic</b>	Headache, depression, psychosis, seizures, cerebritis, transverse myelitis, peripheral neuropathy, stroke

### Investigations

- blood work: ANA (sensitivity 98%, but poor specificity → used as a screening test, ANA titres are not useful to follow disease course)
- anti-dsDNA and anti-Sm are specific (95-99%)
- anti-dsDNA titer and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant
  - anti-dsDNA increases and C3 and C4 decrease with disease activity
- anti-phospholipid antibodies (anti-cardiolipin Ab and lupus anticoagulant), may cause increased risk of clotting and increased aPTT

### Treatment

- **goals of therapy**
  - treat early and avoid long term steroid use, if unavoidable see [Endocrinology](#), E42 for osteoporosis management
  - if high doses of steroids necessary for long-term control, add steroid-sparing agents and taper when possible
  - treatment is tailored to organ system involved and severity of disease
  - all medications used to treat SLE require periodic monitoring for potential toxicity
- **dermatologic**
  - sunscreen, avoid UV light and estrogens
  - topical steroids, hydroxychloroquine
- **musculoskeletal**
  - NSAIDs ± gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
  - hydroxychloroquine improves long term control and prevents flares
  - bisphosphonates, calcium, vitamin D to combat osteoporosis
- **organ-threatening disease**
  - high-dose oral prednisone or IV methylprednisolone in severe disease
  - steroid-sparing agents: azathioprine, methotrexate, mycophenolate
  - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or SLE nephritis)



#### Drug-Induced SLE

Often presents atypically with systemic features and serositis; usually associated with anti-histone antibodies.



#### Raynaud's Phenomenon

Vasospastic disorder characteristically causing discolouration of fingers and toes (white → blue → red). Classic triggers: cold and emotional stress.



## Antiphospholipid Antibody Syndrome (APLA)



### Definition

- multi-system vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions and thrombocytopenia
- often presents with migraine-type headaches
- circulating anti-phospholipid autoantibodies interfere with coagulation cascade
- **primary APLA**: occurs in the absence of other disease
- **secondary APLA**: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- **catastrophic APLA**: development within 1 wk of small vessel thrombotic occlusion in ≥3 organ systems with positive anti-phospholipid antibodies (high mortality)



#### Manifestations of APLA

- Thromboembolic events
- Spontaneous abortions
- Thrombocytopenia
- Associated with livedo reticularis, migraine headaches



Arterial and venous thrombosis are usually mutually exclusive.

**Table 16. Classification Criteria of APLA: 1 clinical and 1 laboratory criteria must be present**

Criteria	Description
<b>CLINICAL</b>	
Vascular thrombosis	Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia Venous: DVT, PE, renal and retinal vein thrombosis Must be confirmed by imaging or histopathology
Pregnancy morbidity	Fetal death (>10 wk GA), recurrent spontaneous abortions (<10 wk GA) or premature birth (<34 wk GA)
<b>LABORATORY</b>	
Lupus anticoagulant	Labs must be positive on 2 occasions, at least 12 wk apart
Anti-cardiolipin Ab	IgG and/or IgM
Anti- $\beta_2$ glycoprotein-I Ab	IgG and/or IgM

J Thromb Haemost 2006;4:295-306

**Signs and Symptoms**

- see clinical criteria in Table 16
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud's phenomenon, purpura, leg ulcers, and gangrene

**Treatment**

- thrombosis
  - lifelong anti-coagulation with warfarin
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent and/or arterial event
- recurrent fetal loss
  - heparin/low molecular weight heparin  $\pm$  Aspirin<sup>®</sup> during pregnancy
- catastrophic APS
  - high-dose steroids, anti-coagulation, cyclophosphamide, plasmapheresis

**A Systematic Review of Secondary Thromboprophylaxis in Patients with Anti-phospholipid Antibodies**

Arthritis Rheum 2007;57:1487-1495

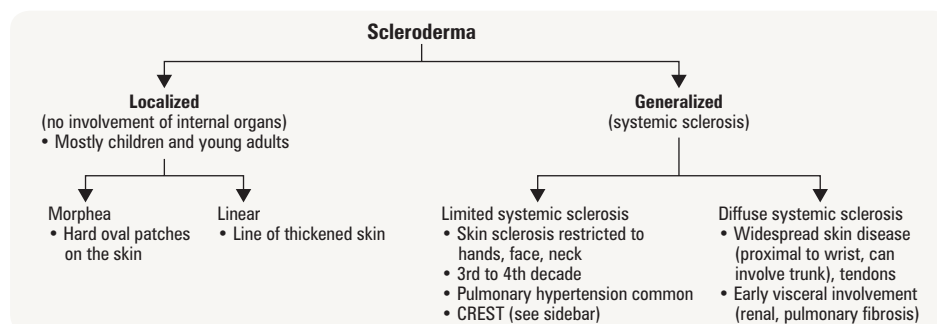
**Study:** Review of RCTs, prospective and retrospective cohort studies, and subgroup analysis (n >15) that focused on the secondary thromboprophylaxis in patients with anti-phospholipid antibodies (aPL) were selected.

**Results:** Sixteen studies were selected. Patients with venous events and a single test for aPL showed a low recurrence rate while receiving oral anti-coagulation at a target INR of 2.0-3.0. Patients with stroke and a single positive aPL test had no increased risk compared with those without aPL. Recurrence rates in patients with definite anti-phospholipid syndrome (APLA) and previous venous thromboembolism were lower than in patients with arterial and/or recurrent events, both with and without therapy. Only 3.8% of recurrent events occurred at an actual INR >3.0. Mortality due to recurrent thrombosis was higher than mortality due to bleeding (18 patients versus 1 patient reported).

**Conclusion:** For patients with definite APLA, the authors recommend prolonged warfarin therapy at a target INR of 2.0-3.0 in APLA patients with first venous events and >3.0 for those with recurrent and/or arterial events. For patients with venous thromboembolism or stroke and a single positive aPL test, the authors recommend further testing to determine if they have a persisting antibody. If they do not, the same therapy as for the general population should be used (warfarin at a target INR of 2.0-3.0 and low-dose Aspirin<sup>®</sup>, respectively).

**Scleroderma****Definition**

- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy and fibrosis

**Figure 9. Forms of scleroderma****CREST Syndrome**

Calcinosis: calcium deposits on skin

Raynaud's phenomenon

Esophageal dysfunction: acid reflux

Sclerodactyly: tightening of skin on digits

Telangiectasia: superficial dilated blood vessels

**Table 17. Classification Criteria of Systemic Sclerosis: 1 major or 2 minor criteria must be present**

Criteria	Description
<b>Major</b>	
Scleroderma proximal to MCPs	Skin tightness, thickening, non-pitting induration
<b>Minor</b>	
Sclerodactyly	Skin changes limited to digits
Digital pitting scars or loss of substance from finger pad	
Bibasilar pulmonary fibrosis	

American Rheumatism Association, 1980

**Etiology and Pathophysiology**

- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
  - intimal proliferation and media mucinous degeneration  $\rightarrow$  progressive obliteration of vessel lumen  $\rightarrow$  fibrotic tissue
  - resembles malignant hypertension



## Epidemiology

- F:M = 3-4:1, peaking in 5th and 6th decades
- associated with HLA-DR1
- associated with environmental exposure (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)
- limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)

## Signs and Symptoms

**Table 18. Clinical Manifestations of Scleroderma**

System	Features
<b>Dermatologic</b>	Painless non-pitting edema → skin tightening Ulcerations, calcinosis, periungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias Characteristic face: mask-like facies with tight lips, beak nose, radial perioral furrows
<b>Vascular</b>	Raynaud's phenomenon → digital pits, gangrene
<b>Gastrointestinal (~90%)</b>	Distal esophageal hypomotility → dysphagia Loss of lower esophageal sphincter function → GERD, ulcerations, strictures Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss Large bowel hypomotility → wide mouth diverticuli are pathognomonic radiographic finding on barium study
<b>Renal</b>	Mild proteinuria, creatinine elevation, hypertension "Scleroderma renal crisis" (10-15%) may lead to malignant arterial hypertension, oliguria and microangiopathic hemolytic anemia
<b>Pulmonary</b>	Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions
<b>Cardiac</b>	Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias
<b>Musculoskeletal</b>	Polyarthralgias "Resorption of distal tufts" (radiological finding) Proximal weakness 2° to disuse, atrophy, low grade myopathy
<b>Endocrine</b>	Hypothyroidism

## Investigations

- bloodwork
  - CBC, Cr, ANA
  - anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis
  - anti-centromere: favours diagnosis of CREST (limited systemic sclerosis)
- PFT
  - assess for pulmonary hypertension or interstitial lung disease
- imaging
  - CXR for fibrosis, echo for pulmonary HTN

## Treatment

- dermatologic
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), methotrexate (limited evidence)
- vascular
  - patient education on cold avoidance
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE<sub>2</sub> inhibitors, PDE5 inhibitors)
- gastrointestinal
  - GERD: PPIs are first line, then H<sub>2</sub>-receptor agonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
- renal disease
  - ACE inhibitors for hypertensive crisis
- pulmonary
  - early interstitial disease: cyclophosphamide
  - pulmonary hypertension: vasodilators e.g. bosentan (Tracleer®), epoprostenol (Flolan®), PDE5 inhibitors
- cardiac
  - pericarditis: systemic steroids
- musculoskeletal
  - arthritis: NSAIDs
  - myositis: systemic steroids



### Raynaud's Phenomenon DDX

#### COLD HAND

Cryoglobulins/Cryofibrinogens  
Obstruction/Occupational  
Lupus erythematosus, other connective tissue disease  
Diabetes mellitus/Drugs  
Hematologic problems (polycythemia, leukemia, etc.)  
Arterial problems (atherosclerosis)/  
Anorexia nervosa  
Neurologic problems (vascular tone)  
Disease of unknown origin (idiopathic)



Scleroderma is the most common cause of secondary Raynaud's phenomenon.



Lung disease is the most common cause of morbidity and mortality.



### Features of Pathologic Raynaud's Syndrome

- New onset
- Asymmetric
- Precipitated by stimuli other than cold
- Associated with distal pulp pitting or tissue reabsorption
- Digit ischemia
- Capillary dilatation by capillaroscopy

## Idiopathic Inflammatory Myopathy



### Definition

- autoimmune diseases characterized by proximal muscle weakness  $\pm$  pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process
- classification
  - polymyositis (PM)/dermatomyositis (DM) (see Table 19)
    - adult and juvenile form
    - associated with malignancy
      - ♦ increased risk of malignancy: age >50, DM>PM, normal CK, refractory disease
      - ♦ 2.4-6.5 fold increased risk of underlying malignancy usually in internal organs
  - associated with other connective tissue disease
  - inclusion body myositis (IBM)
    - ♦ age >50, M>F, slowly progressive, vacuoles in cells on biopsy
    - ♦ suspect when patient unresponsive to treatment
    - ♦ distal as well as proximal muscle weakness
    - ♦ muscle biopsy positive for inclusion bodies

### POLYMYOSITIS (PM)/DERMATOMYOSITIS (DM)

**Table 19. Classification Criteria for PM/DM. Definite if 4 present, probable if 3 present.**

Criteria	Description
1. Symmetric proximal muscle weakness	Typical involvement of shoulder girdle and hip girdle
2. Elevated muscle enzymes	$\uparrow$ CK, aldolase, LDH, AST, ALT
3. EMG changes	Short polyphasic motor units, high frequency repetitive discharge, insertional irritability
4. Muscle biopsy	Segmental fibre necrosis, basophilic regeneration, perivascular inflammation (DM), endomysial inflammation (PM) and atrophy
5. Typical rash of dermatomyositis	Required for diagnosis of DM (see below)

NEJM 1975;292:403-407

### Etiology and Pathophysiology

- PM is CD8 cell-mediated muscle necrosis, found in adults
- DM is B-cell and CD4 immune complex-mediated peri-fascicular vascular abnormalities

### Signs and Symptoms

- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over weeks to months
  - difficulty lifting head off pillow, arising from chair, climbing stairs
- dermatological
  - DM has characteristic dermatological features (F>M, children and adults)
    - ♦ Gottron's papules
      - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
    - ♦ Gottron's sign
      - erythematous, smooth or scaly patches over the dorsal IPs, MCPs, elbows, knees, or medial malleoli
    - ♦ heliotrope rash: violaceous rash over the eyelids; usually with edema
    - ♦ shawl sign: erythematous rash over neck, upper chest, and shoulders
    - ♦ mechanic's hands: dark, dry, thick scale on palmar and lateral surface of digits
    - ♦ periungual erythema
- cardiac
  - dysrhythmias, CHF, conduction defect, ventricular hypertrophy, pericarditis
- gastrointestinal
  - oropharyngeal and lower esophageal dysphagia, reflux
- pulmonary
  - weakness of respiratory muscles, interstitial lung disease, aspiration pneumonia



#### Signs of DM

Gottron's papules and Gottron's sign are pathognomonic of DM (occur in 70% of patients).



### Investigations

- bloodwork: CK, ANA, anti-Jo-1 (DM), anti-Mi-2, anti-SRP
- imaging: MRI may be used to localize biopsy site
- EMG, muscle biopsy

### Treatment

- non-pharm: physical therapy and occupational therapy
- pharmacologic treatment:
  - high-dose corticosteroid (1-2 mg/kg/d) and slow taper
  - add immunosuppressive agents (azathioprine, methotrexate, cyclosporine)
  - intravenous immunoglobulin if severe or refractory
  - hydroxychloroquine for DM rash

- malignancy surveillance
  - detailed history and physical (breast, pelvic and rectal exam)
  - CXR, abdominal and pelvic ultrasound, fecal occult blood, Pap test, mammogram ± CT scan (thoracic, abdominal, pelvic)


**Malignancies Associated with DM**

- Breast
- Lung
- Colon
- Ovarian

## Sjögren's Syndrome (SS)

### Definition

- autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca/xerophthalmia) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
- may evolve into systemic disorder with diminished exocrine gland activity in respiratory tract and skin
- primary and secondary form (associated with RA, SLE, DM and HIV)
- incidence estimated at 4/100,000 people
- 90% of cases are among females
- mean age of diagnosis is 40-60 yr

**Table 20. Classification Criteria for SS. Need 4 present, one of which includes salivary gland biopsy or autoantibodies**

Criteria	Description
1. Dry eye symptoms	Dry >3 mo, foreign body sensation, or requiring tear substitutes
2. Dry mouth symptoms	Dry >3 mo, swollen salivary glands, or requiring liquids to swallow food
3. Dry eye signs	Schirmer test (to assess tear flow) or slit lamp exam with Rose Bengal stain
4. Dry mouth signs	Low salivary flow, sialography
5. Salivary gland biopsy	Focal lymphocytic sialoadenitis
6. Autoantibodies	anti-Ro and/or anti-La, ANA, RF

Ann Rheum Dis 2002;61:554-558

### Signs and Symptoms

- "sicca complex": dry eyes (keratoconjunctivitis sicca/xerophthalmia), dry mouth (xerostomia)
- staphylococcus blepharitis
- dental caries, oral candidiasis, angular cheilitis (inflammation and fissuring at the labial commissures of the mouth)
- systemic complications
  - sinusitis, autoimmune thyroid dysfunction
  - arthralgias, arthritis
  - subclinical diffuse interstitial lung disease, xerotrachea leading to chronic dry cough
  - renal disease, glomerulonephritis
  - palpable purpura, vasculitis
  - peripheral neuropathy
  - lymphoma risk greatly increased

### Treatment

- ocular
  - artificial tears or surgical punctal occlusion for dry eyes
- oral
  - good dental hygiene, hydration
  - agents that stimulate salivary flow (e.g. pilocarpine)
  - topical nystatin or clotrimazole x 4-6 wk for oral candidiasis
- systemic
  - e.g. hydroxychloroquine, corticosteroids


**Classic Triad (identifies 93% of Sjögren's patients)**

- Dry eyes
- Dry mouth (xerostomia) → dysphagia
- Arthritis (small joint, asymmetrical, non-erosive) but may be associated with rheumatoid arthritis, in which case, the arthritis is erosive



Patients with Sjögren's syndrome are at higher risk of non-Hodgkin's lymphoma.

## Mixed Connective Tissue Disease (MCTD)/Overlap Syndrome

- syndrome with features of 3 different CTD (e.g. SLE, scleroderma, PM)
- common symptoms: Raynaud's phenomenon, swollen fingers
- bloodwork: anti-RNP (see Table 10)
- treatment is generally guided by the severity of symptoms and organ system involvement
- prognosis
  - 50-60% will evolve into SLE
  - 40% will evolve into scleroderma
  - only 10% will remain as MCTD for the rest of their lives
  - cardiac involvement (dysrhythmia) common, renal or lung involvement rare

# Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction
- any organ system can be involved
- keys to diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection
  - labs non-specific: anemia, increased WBC and ESR, abnormal urinalysis
  - biopsy if tissue accessible
  - angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressive agents

**Table 21. Classification of Vasculitis and Characteristic Features**

Classification	Characteristic Features
<b>SMALL VESSEL</b>	
<ul style="list-style-type: none"> <li>• <b>Non-ANCA-associated</b> <ul style="list-style-type: none"> <li>Predominantly cutaneous vasculitis</li> <li>Henoch-Schönlein purpura (see <a href="#">Pediatrics</a>, P99)</li> <li>Essential cryoglobulinemic vasculitis</li> </ul> </li> </ul>	<p>Immune complex-mediated (most common mechanism)</p> <p>Also known as hypersensitivity/leukocytoclastic vasculitis</p> <p>Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting; most common in childhood</p> <p>Systemic vasculitis caused by circulating cryoproteins forming immune complexes. May be associated with underlying infection (e.g. hepatitis C) or connective tissue disease.</p>
<ul style="list-style-type: none"> <li>• <b>ANCA-associated</b> <ul style="list-style-type: none"> <li>Granulomatosis with polyangiitis (GPA, formerly Wegener's)</li> <li>pR3 (c-ANCA) &gt; MPO (p-ANCA)</li> <li>Eosinophilic granulomatosis with polyangiitis (EPGA or Churg-Strauss syndrome) (50% ANCA positive)</li> <li>Microangiopathic polyangiitis (70% ANCA positive, usually MPO)</li> </ul> </li> </ul>	<p>Granulomatous inflammation of vessels of respiratory tract and kidneys, initially have URTI symptoms; most common in middle age</p> <p>Granulomatous inflammation of vessels with hypereosinophilia and eosinophilic tissue infiltration, frequent lung involvement (asthma, allergic rhinitis), can be associated with MPO or pR3, other manifestations include coronary arteritis, myocarditis and neuropathy, average age 40s</p> <p>Pauci-immune necrotizing vasculitis, affecting kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin, most common in middle age</p>
<b>MEDIUM VESSEL</b>	
<ul style="list-style-type: none"> <li>Polyarteritis nodosa</li> <li>Kawasaki's (see <a href="#">Pediatrics</a>, P100)</li> </ul>	<p>Segmental, non-granulomatous necrotizing inflammation</p> <p>Unknown etiology in most cases, any age (average 40-50s), M&gt;F</p> <p>T lymphocyte response and granuloma formation</p>
<b>LARGE VESSEL</b>	
<ul style="list-style-type: none"> <li>Giant cell arteritis (GCA) /Temporal Arteritis</li> <li>Takayasu's arteritis</li> </ul>	<p>Inflammation predominantly of the aorta and arteries originating from it</p> <p>Over 50 yr of age, F&gt;M</p> <p>"Pulseless disease", unequal peripheral pulses, chronic inflammation, most often the aorta and its branches</p> <p>Usually young adults of Asian descent, F&gt;M; risk of aortic aneurysm</p>
<b>OTHER VASCULITIDES</b>	
<ul style="list-style-type: none"> <li>Buerger's disease ("Thromboangiitis Obliterans")</li> <li>Behçet's disease</li> <li>Vasculitis mimicry</li> </ul>	<p>Inflammation secondary to pathological clotting, affects small and medium-sized vessels of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking</p> <p>Most common in young Asian males</p> <p>Leukocytoclastic vasculitis, multi-system disorder presenting with ocular involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement, more common in Mediterranean and Asia, average age 30s, M&gt;F</p> <p>Cholesterol emboli, atrial myxoma</p>



**c-ANCA:** circulating anti-neutrophil cytoplasmic antibody associated with anti PR3.

**p-ANCA:** perinuclear anti-neutrophil cytoplasmic antibody associated with multiple antigens, e.g. lactoferrin (IBD), myeloperoxidase (microscopic polyangiitis).



## Features of Small Vessel Vasculitis

- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers



## Churg-Strauss Triad

- Allergic rhinitis and asthma (often quiescent at time of vasculitis)
- Eosinophilic infiltrative disease resembling pneumonia
- Systemic vasculitis often mononeuritis multiplex/peripheral neuropathy and peripheral eosinophilia



## Features of Medium Vessel Vasculitis

- Livedo reticularis
- Erythema nodosum
- Raynaud's phenomenon
- Nodules
- Digital infarcts
- Ulcers



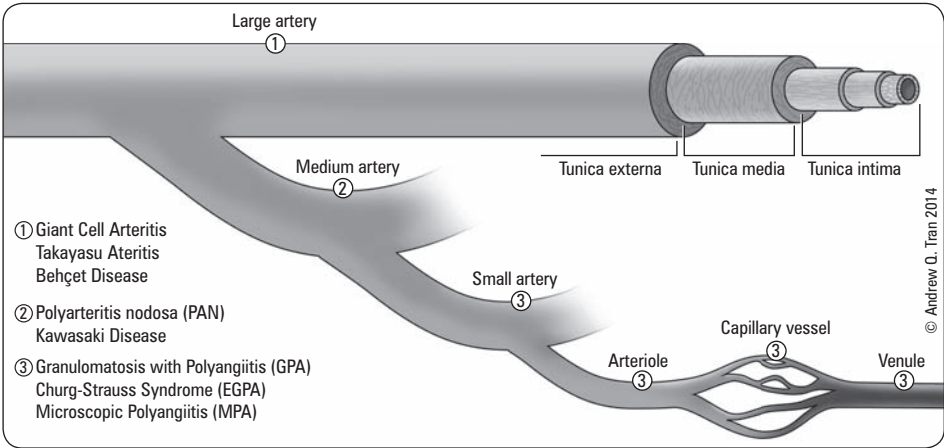


Figure 10. Classification of vasculitides by vessel size

Small Vessel Non-ANCA Associated Vasculitis

PREDOMINANTLY CUTANEOUS VASCULITIS

- subdivided into
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases

Etiology and Pathophysiology

- cutaneous vasculitis following
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes
- small vessels involved (post-capillary vessels most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Signs and Symptoms

- palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules

Investigations

- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment

- stop possible offending drug
- corticosteroids ± immunosuppressive agents
- usually self-limiting

Small Vessel ANCA-Associated Vasculitis

GRANULOMATOSIS WITH POLYANGIITIS (formerly known as Wegener’s Granulomatosis)

Definition

- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA
- incidence 5 per 100,000; more common in Northern latitudes

Table 22. Classification Criteria for GPA. Diagnosed if 2 or more of the following 4 criteria present.

Criteria	Description
1. Nasal or oral involvement	Inflammation, ulcers, epistaxis
2. Abnormal findings on CXR	Nodules, cavitations, etc.
3. Urinary sediment	Protein, RBC casts
4. Biopsy of involved tissue	Lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis

## Etiology

- pathology is complex, possibly involving transformation from inflammatory prodrome (serous otitis media and sinusitis) to full-blown vasculitic syndrome

## Signs and Symptoms

- systemic
  - malaise, fever, weakness, weight loss
- HEENT
  - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
  - proptosis due to: inflammation/vasculitis involving extra-ocular muscles, retrobulbar space occupying lesions or direct extension of masses from the upper respiratory tract
  - hearing loss due to involvement of CN VIII
- pulmonary
  - cough, hemoptysis
- renal
  - hematuria
- other
  - joint, skin, eye complaints, vasculitic neuropathy

## Investigations

- bloodwork: anemia (normal MCV), increased WBC, increased Cr, increased ESR, ANCA pR3 > MPO
- urinalysis: proteinuria, hematuria, RBC casts
- CXR: pneumonitis, lung nodules, infiltrations, cavitory lesions
- biopsy: renal (segmental necrotizing glomerulonephritis), lung (granulomas, tracheobronchial erosion)
- possible decline in c-ANCA and ESR used to monitor response to treatment in some patients

## Treatment

- prednisone 1 mg/kg/d PO for 3-6 mo  $\pm$  cyclophosphamide 2 mg/kg/d PO for 3-6 mo followed by high dose methotrexate (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/d PO once daily)
- consider biologic agents (rituximab, IVIG) and plasmapheresis (PEXIVAS trial)
- RAVE trial (NEJM 2010; 363:221-232): rituximab equivalent or superior to cyclophosphamide with less toxicity



### Classic Features

- Necrotizing granulomatous vasculitis of lower and upper respiratory tract
- Focal segmental glomerulonephritis

# Medium Vessel Vasculitis

## POLYARTERITIS NODOSA (PAN)

### Definition

- systemic, necrotizing vasculitis of medium sized vessels
- ANCA negative
- often associated with hepatitis B positivity
- incidence 0.7 per 100,000; affects individuals between 40-60 yr; M:F = 2:1

**Table 23. Classification Criteria for PAN. Diagnosed if 3 or more of the following 10 criteria present.**

Criteria	Description
1. Weight loss	>4 kg, not due to dieting or other factors
2. Myalgias, weakness or leg tenderness	Diffuse myalgias or weakness
3. Livedo reticularis	Mottled, reticular pattern over skin
4. Neuropathy	Mononeuropathy, mononeuropathy multiplex or polyneuropathy
5. Testicular pain or tenderness	Not due to infection, trauma or other causes
6. dBP >90 mmHg	Development of hypertension with dBP >90 mmHg
7. Elevated Cr or BUN	Cr >130 $\mu$ mol/L (1.5 mg/dL), BUN >14.3 mmol/L (40 mg/dL)
8. Hepatitis B positive	Presence of Hepatitis B surface antigen or antibody
9. Arteriographic abnormality	Commonly aneurysms
10. Biopsy of artery	Presence of granulocytes and/or mononuclear leukocytes in the artery wall

American College of Rheumatology, 1990

## Etiology and Pathophysiology

- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion



There is an association between hepatitis B surface antigen (HBsAg) positivity and PAN.



Consider PAN in a non-diabetic patient with mononeuritis multiplex.

**Investigations**

- bloodwork: CBC, ESR, Cr, BUN, p-ANCA, hepatitis B serology
- imaging: angiography
- arterial biopsy

**Treatment**

- prednisone 1 mg/kg/d PO and cyclophosphamide 2 mg/kg/d PO
- ± anti-viral therapy to enhance clearance of HBV

## Large Vessel Vasculitis

- please see [Neurology](#), N39 and [Ophthalmology](#), OP38 for more details

**GIANT CELL ARTERITIS (GCA)/TEMPORAL ARTERITIS****Table 24. Classification Criteria for GCA. Diagnosed if 3 or more of the following 5 criteria present.**

Criteria	Description
1. Age at onset >50	
2. New headache	Often temporal
3. Temporal artery abnormality	Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis
4. Elevated ESR	ESR >50 mm/h
5. Abnormal artery biopsy	Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

American College of Rheumatology, 1990

**GCA Criteria**

Presence of 3 or more criteria yields sensitivity of 94%, specificity of 91%.

**Epidemiology**

- most frequent vasculitis in North America
- patients >50 yr
- F:M = 2:1
- North-South gradient (predominance in Northern Europe/US)
- affects extracranial arteries

**Signs and Symptoms**

- new onset temporal headache ± scalp tenderness due to inflammation of involved portion of the temporal or occipital arteries
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
- tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
- polymyalgia rheumatica (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta result in pulseless disease), aortic aneurysm ± rupture are late complications

**Medical Emergency**

Untreated, GCA can lead to permanent blindness in 20-25% of patients!  
Treat on clinical suspicion.

**Investigations**

- diagnosis made by clinical suspicion, increased ESR, increased CRP, temporal artery biopsy within 14 d of starting steroids, possible ultrasound

**Treatment**

- if suspect GCA, immediately start high dose prednisone 1 mg/kg in divided doses for approximately 4 wk, and then tapering prednisone as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
- consider low dose ASA

**Prognosis**

- increased risk of thoracic aortic aneurysm and aortic dissection
- yearly CXR ± abdominal ultrasound as screening

SERONEGATIVE RHEUMATIC DISEASE

Spondyloarthropathies

Table 25. A Comparison of the Spondyloarthropathies (inflammatory joint disease of the vertebral column)

Feature	Ankylosing Spondylitis	Psoriatic Arthritis	Reactive Arthritis	Enteropathic Arthritis
M:F	3:1	1:1	8:1	1:1
Age of onset	20s	35-45	20s	Any
Peripheral arthritis	25%	96%	90%	Common
Distribution	Axial, LE	Any	LE	LE
Sacroiliitis	100%	40%	80%	20%
Dactylitis	Uncommon	Occasional	Common	Uncommon
Enthesitis	Common	Common	Common	Less Common
Skin lesions	Rare	100% Psoriasis eventually 70% at onset of arthritis	Common Keratoderma	Occasional Pyoderma, erythema nodosum
Uveitis	30%	Occasional	20%	Rare
Urethritis	Rare	Occasional	Common	Rare
HLA-B27	90%	40%	80%	30%

LE = lower extremities

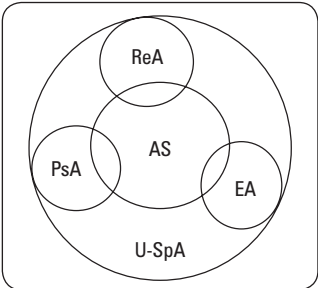


Figure 11. Spondyloarthropathy subsets (U-SpA = undifferentiated spondyloarthropathy)

Ankylosing Spondylitis (AS)

Definition

- chronic inflammatory arthritis involving the sacroiliac joints and vertebrae (see Figure 12)
- AS in women: more peripheral arthritis and upper spine spondylitis
- prototype of the spondyloarthropathies

Table 26. ASAS Classification Criteria for Axial Spondyloarthritis (for patients with ≥3 months back pain and age at onset <45 years)

Sacroiliitis on imaging plus ≥1 SpA feature or HLA B-27 positive plus ≥2 SpA features	
<b>SpA features:</b> <ul style="list-style-type: none"><li>• Inflammatory back pain</li><li>• Arthritis</li><li>• Enthesitis (heel)</li><li>• Uveitis</li><li>• Dactylitis</li><li>• Psoriasis</li><li>• Crohn's disease/colitis</li><li>• Good response to NSAIDs</li><li>• Family history of SpA</li><li>• HLA-B27 positive</li><li>• Elevated CRP</li></ul>	<b>Sacroiliitis on imaging:</b> <ul style="list-style-type: none"><li>• Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA</li><li>• Definite radiographic sacroiliitis according to modified NY criteria</li></ul>

Etiology and Pathophysiology

- enthesitis (inflammation of tendon or ligament at site of attachment to bone)
- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

Epidemiology

- M:F = 5:1; females have milder disease which may be under-recognized
- 95% of patients have HLA-B27 (9% HLA-B27 positive in general population)

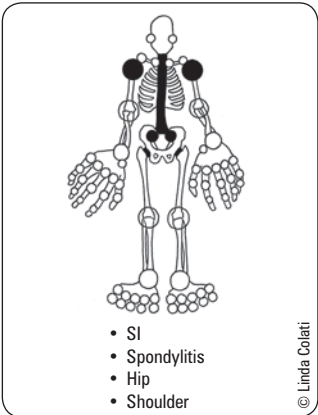


Figure 12. Common sites of involvement of AS



**Rule of 2s**  
**AS occurs in**  
0.2% of the general population  
2% of HLA-B27 positive individuals  
20% of HLA-B27 positive individuals with affected family member

Table 27. Types of Back Pain

Parameter	Mechanical	Inflammatory
Past History	±	++
Family History	–	+
Onset	Acute	Insidious
Age (years)	15-90	<40
Sleep Disturbance	±	++ (worse during 2nd half of night)
Morning Stiffness	<30 min	>1 h
Involvement of Other Systems	–	+
Exercise	Worse	Better
Rest	Better	Worse
Radiation of Pain	Anatomic (L5-S1)	Diffuse (thoracic, buttock)
Sensory Symptoms	+	–
Motor Symptoms	+	–

## Signs and Symptoms

### • axial

- mid and lower back stiffness, prolonged morning stiffness, night pain, persistent buttock pain, painful sacroiliac joint (+ Faber test) (see Table 27)
- spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion, normal >5 cm at T4), cervical (global decrease, often extension first)
- postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance (>5 cm)

### • peripheral

- asymmetrical large joint arthritis, most often involving lower limb
- enthesitis: tenderness over tibial tuberosity, or Achilles tendon and plantar fascia insertions into the calcaneus

### • extra-articular manifestations

- ophthalmic: acute anterior uveitis is common (25-30% patients)
- renal: amyloidosis (late and rare) and IgA nephropathy
- gastrointestinal: inflammatory bowel disease
- cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
- respiratory: apical fibrosis (rare)
- neurologic: cauda equina syndrome (rare)
- skin: psoriasis

## Investigations

- x-ray of SI joint: “pseudowidening” of joint due to erosion with joint sclerosis → bony fusion (late), symmetric sacroiliitis
- x-ray of spine: “squaring of edges” from erosion and sclerosis on corners of vertebral bodies (shiny corner sign) leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes) → “bamboo spine” radiographically
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes. Best seen on T2 STIR images (suppress fat and see bone edema)

## Treatment

### • conservative/non-pharmacologic

- prevent fusion from poor posture and disability through: exercise (e.g. swimming), postural and deep breathing exercises, outpatient PT, smoking cessation

### • medical

- NSAIDs (first line of treatment)
- glucocorticoids (topical eye drops, local injections)
- DMARDs for peripheral arthritis (sulfasalazine, methotrexate)
- biologics for axial and peripheral involvement
- manage extra-articular manifestations

### • surgical

- hip replacement, vertebral osteotomy for marked deformity

## Prognosis

- spontaneous remissions and relapses are common and can occur at any age
- function may be excellent despite spinal deformity
- favourable prognosis if female and age of onset >40 yr
- early onset with hip disease may lead to severe disability; may require arthroplasty



### Extra-articular Manifestations of AS

#### 6 As

Atlanto-axial subluxation  
Anterior uveitis  
Apical lung fibrosis  
Aortic incompetence  
Amyloidosis (kidneys)  
Autoimmune bowel disease (UC)



Consider AS in the differential for causes of aortic regurgitation.



The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a self-reported scoring system that focuses on fatigue, axial pain, peripheral pain, enthesitis, and morning stiffness.

## Enteropathic Arthritis (EA)

- see [Gastroenterology](#), *Inflammatory Bowel Disease*, G19
- MSK manifestations in the setting of either ulcerative colitis (UC) or Crohn's disease (CD) include peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthropathy
- arthralgia, myalgia, osteoporosis and aseptic necrosis of bone 2° to steroid treatment of bowel inflammation
- NSAIDs should be used cautiously as they may exacerbate bowel disease

**Table 28. Comparing Features of Spondylitis vs. Peripheral Arthritis in EA**

Parameter	Spondylitis	Peripheral Arthritis
HLA-B27 association	Yes	No
Gender	M>F	M=F
Onset before IBD	Yes	No
Parallels IBD course	No	Yes
Type of IBD	UC=CD	CD



Both AS and EA feature symmetric sacroiliitis.

## Psoriatic Arthritis (PsA)

### Etiology and Pathophysiology

- unclear but many genetic, immunologic and some environmental factors involved (e.g. psoriatic plaque flora, particularly Group A *Streptococcus*, and trauma)

### Epidemiology

- psoriasis affects 1% of population
- arthropathy in 10% of patients with psoriasis
- 15-20% of patients will develop joint disease before skin lesions appear

### Signs and Symptoms

- **dermatologic**
  - well-demarcated erythematous plaques with silvery scale
  - nail involvement: pitting, transverse or longitudinal ridging, discolouration, subungual hyperkeratosis, onycholysis, and oil drops
- **musculoskeletal**
  - 5 general patterns
    - ♦ asymmetric oligoarthritis (most common – 70%)
    - ♦ arthritis of DIP joints with nail changes
    - ♦ destructive (mutilans) arthritis (5%)
    - ♦ symmetric polyarthritis (similar to RA)
    - ♦ sacroiliitis and spondylitis (usually older, male patients)
  - other findings: dactylitis, enthesopathy
- **ophthalmic**
  - conjunctivitis, iritis (anterior uveitis)
- **cardiac and respiratory** (late findings)
  - aortic insufficiency
  - apical lung fibrosis
- **neurologic**
  - cauda equina syndrome
- **radiologic**
  - floating syndesmophytes
  - pencil-in-cup appearance at IP joints
  - osteolysis, periostitis

### Treatment

- treat skin lesions (e.g. steroid cream, salicylic and/or retinoic acid, tar, UV light)
- NSAIDs or intra-articular steroids
- DMARDs, biologic therapies to minimize erosive disease (use early if peripheral joint involvement)



Check “hidden” areas for psoriatic lesions (ears, hair line, umbilicus, gluteal cleft, nails).



**Risks and Benefits of Tumour Necrosis Factor- $\alpha$  Inhibitors in the Management of Psoriatic Arthritis (PsA): Systematic Review and Meta-analysis of Randomized Controlled Trials**  
*J Rheumatol* 2008;35:883-890

**Study:** Review of RCTs of adalimumab, etanercept, and infliximab used in patients with PsA.

**Results:** Six RCTs were included (n=982). All 3 TNF $\alpha$  inhibitors were significantly more effective than placebo on the basis of Psoriatic Arthritis Response Criteria (PsARC) and American College of Rheumatology response criteria ACR20, ACR50, and ACR70 ratings. There were no significant differences between TNF- $\alpha$  inhibitors and placebo in the proportions of patients who withdrew for any reason (RR 0.48, 95% CI 0.20-1.18), or withdrawal due to adverse events (RR 2.14, 95% CI 0.73-6.27), serious adverse events (RR 0.98, 95% CI 0.55-1.77), or upper respiratory tract infections (RR 0.91, 95% CI 0.65-1.28). Pooled rates for injection site reactions were significantly higher for adalimumab and etanercept than for placebo (RR 2.48, 95% CI 1.16-5.29), but there was no significant difference in the proportion of patients experiencing infusion reactions with infliximab (RR 1.03, 95% CI 0.48-2.20) compared to placebo. Indirect analysis did not demonstrate any significant differences between the TNF- $\alpha$  inhibitors.

**Conclusions:** TNF- $\alpha$  inhibitors are effective treatments for PsA with no important added risks associated with their short-term use. There is still a need for long-term risk-benefit assessment of use of these drugs for the management of PsA.

## Reactive Arthritis (ReA)

### Definition

- two meanings
  1. Reactive arthritis: a sterile arthritis following an infection (e.g. rheumatic fever, post-viral arthritis, etc.), not used frequently by rheumatologists
  2. Reactive Arthritis (ReA): one of the seronegative spondyloarthropathies in which patients have a peripheral arthritis ( $\geq 1$  mo duration) accompanied by one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tracts



### Etiology

- onset following an infectious episode either involving the GI or GU tract
  - GI: *Shigella*, *Salmonella*, *Campylobacter*, *Yersinia* species
  - GU: *Chlamydia* (isolated in 16-44% of ReA cases), *Mycoplasma* species
- acute clinical course
  - 1-4 wk post-infection
  - lasts weeks to years
  - often recurring
  - spinal involvement persists

### Epidemiology

- in HLA-B27 patients, axial > peripheral involvement
- M>F

### Signs and Symptoms

- musculoskeletal**
  - peripheral arthritis, asymmetric pattern, spondylitis, Achilles tendinitis, plantar fasciitis, dactylitis
- ophthalmic**
  - iritis (anterior uveitis), conjunctivitis
- dermatologic**
  - keratoderma blenorrhagicum (hyperkeratotic skin lesions on palms and soles) and balanitis circinata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- gastrointestinal**
  - oral ulcers, diarrhea
- urethritis and cervicitis**
  - sterile cultures; presence not related to site of initiating infection

### Investigations

- diagnosis is clinical plus laboratory
- bloodwork: normocytic, normochromic anemia and leukocytosis
- sterile cultures
- serology: HLA-B27 positive

### Treatment

- antibiotics for non-articular infections
- NSAIDs, physical therapy, exercise
- local therapy
  - joint protection
  - intra-articular steroid injection
  - topical steroid for ocular involvement
- systemic therapy
  - corticosteroids, sulfasalazine, methotrexate (for peripheral joint involvement only)
  - TNF- $\alpha$  inhibitors for spinal inflammation

### Prognosis

- self-limited, typically 3-5 mo, varies based on pathogen and patient's genetic background
- chronic in 15-20% of cases



#### Clinical triad of reactive arthritis:

- Arthritis
- Conjunctivitis
- Urethritis/cervicitis



#### "Can't see, can't pee, can't climb a tree":

Triad of conjunctivitis, urethritis, and arthritis is 99% specific (but 51% sensitive) for ReA.

## Crystal-Induced Arthropathies



Table 29. Gout vs. Pseudogout

Parameter	Gout	Pseudogout
Gender	M>F	M=F
Age	Middle-aged males Post-menopausal females	Age >60
Onset of disease	Acute	Acute/insidious
Crystal type	Monosodium urate (MSU) Negative birefringence (yellow when parallel to compensator filter), needle-shaped	Calcium pyrophosphate dihydrate (CPPD) Positive birefringence (blue when parallel), rhomboid-shaped
Distribution	First MTP classically; also midfoot, ankle, knee, or polyarticular	Knee, wrist; typically monoarticular
Radiology (note findings are non-specific)	Erosions	Chondrocalcinosis OA (knee, wrist, 2nd and 3rd MCP)
Treatment	NSAIDs, corticosteroids, colchicine, Allopurinol, febuxostat	NSAIDs, corticosteroids



## Gout

### Definition

- derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

### Etiology and Pathogenesis

- sources of uric acid: diet and endogenous
- synthesis
  - hypoxanthine → xanthine → uric acid
  - both steps catalyzed by xanthine oxidase

### Hyperuricemia

- primary or genetic**
  - mostly due to idiopathic renal underexcretion (90%)
  - also idiopathic overproduction or abnormal enzyme production/function
- secondary**
  - dietary excess (particularly high consumption of beer, seafood, and meat)
  - underexcretion (>90%): renal failure, drugs, systemic conditions
  - overproduction (<10%): increased nucleic acid turnover states (e.g. malignancy, post-chemotherapy)
- sudden changes (increasing or decreasing) in uric acid concentration are more important than absolute values
  - acute gout can occur with normal serum uric acid
  - changes in pH, temperature or initiation of antihyperuricemics may precipitate an acute gouty attack
- common precipitants: alcohol, dietary excess, dehydration, drugs (e.g. thiazide and loop diuretics), trauma, illness, surgery, starting xanthine oxidase inhibitor therapy
- other associated conditions: hypertension, obesity, diabetes, starvation

### Epidemiology

- most common in males >45 yr old
- extremely rare in premenopausal female

### Signs and Symptoms

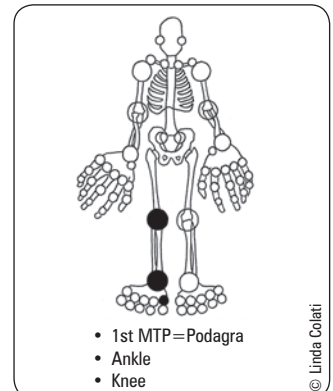
- single episode progressing to recurrent episodes of acute inflammatory arthritis
- acute gouty arthritis**
  - severe pain, redness, joint swelling, usually involving lower extremities (see Figure 13)
  - joint mobility may be limited
  - attack will subside spontaneously within several days to weeks; may recur
- tophi**
  - urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
  - common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
- kidney**
  - gouty nephropathy
  - uric acid calculi

### Investigations

- joint aspirate: >90% of joint aspirates show crystals of monosodium urate (see Table 29) (negatively birefringent, needle-shaped)
- x-rays may show tophi as soft tissue swelling, punched-out lesions – erosion with “overhanging” edge

### Treatment

- acute gout**
  - NSAIDs: high dose, then taper as symptoms improve
  - corticosteroids: intra-articular, oral or intra-muscular (if renal, cardiovascular, or GI disease and/or if NSAIDs contraindicated or failed)
  - colchicine within first 12 h but effectiveness limited by narrow therapeutic range
  - allopurinol can worsen an acute attack (do not start during acute flare)
- chronic gout**
  - conservative
    - avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
    - avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)
  - medical
    - antihyperuricemic drugs (allopurinol and febuxostat): decrease uric acid production by inhibiting xanthine oxidase
    - uricosuric drugs (probenecid, sulfinpyrazone): use if failure on or intolerant to allopurinol; do not use in renal failure
    - prophylaxis prior to starting antihyperuricemic drugs (colchicine/low-dose NSAID)
    - in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor creatinine
- indications for treatment with antihyperuricemic medications include:
  - recurrent attacks, tophi, bone erosions, urate kidney stones. Perhaps in renal dysfunction with very high urate load (controversial)



**Figure 13. Common sites of involvement in gout**  
(asymmetric joint involvement)



An acute gout attack may mimic cellulitis. However, joint mobility is preserved in cellulitis. Gout often affects more than one joint (i.e. ankle, midfoot and MTPs).



#### Precipitants of Gout

##### Drugs are FACT

Furosemide  
Aspirin®/Alcohol  
Cytotoxic drugs  
Thiazide diuretics

##### Foods are SALT

Seafood  
Alcohol (beer and spirits)  
Liver and kidney  
Turkey (meat)



- The majority of people with hyperuricemia do not have gout
- Normal or low uric acid levels do not rule out gout

## Pseudogout (Calcium Pyrophosphate Dihydrate Disease)

### Etiology and Pathophysiology

- acute inflammatory arthritis due to phagocytosis of IgG-coated calcium pyrophosphate dihydrate (CPPD) crystals by neutrophils and subsequent release of inflammatory mediators within joint space

### Epidemiology

- more frequently polyarticular
- slower in onset in comparison to gout, lasts up to 3 wk but is self-limited

### Risk Factors

- old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), diabetes, hemochromatosis

### Signs and Symptoms

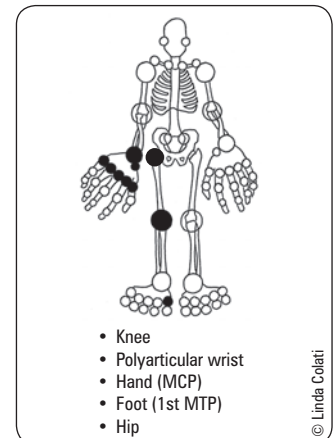
- affects knees, wrists, MCPs, hips, shoulders, elbows, ankles, big toe (see Figure 14)
- multiple manifestations:
  - asymptomatic crystal deposition (seen on radiograph only)
  - acute crystal arthritis (self-limited flares of acute inflammatory arthritis resembling gout)
  - pseudo-osteoarthritis (progressive joint degeneration, sometimes with episodes of acute inflammatory arthritis)
  - pseudo-rheumatoid arthritis (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- acute may be triggered by dehydration, acute illness, surgery, trauma

### Investigations

- must aspirate joint to rule out septic arthritis, gout
- CPPD crystals: present in 60% of patients, often only a few crystals
- x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

### Treatment

- joint aspiration, rest, and protection
- NSAIDs: also used for maintenance therapy
- prophylactic colchicine PO (controversial)
- intra-articular or oral steroids to relieve inflammation



**Figure 14. Common sites of involvement in CPPD**

## Pediatric Rheumatology

- see [Pediatrics](#), P96



## Non-Articular Rheumatism

### Definition

- disorders that primarily affect soft tissues or periarticular structures
- includes bursitis, tendinitis, tenosynovitis, fibromyalgia, and polymyalgia rheumatica

## Polymyalgia Rheumatica (PMR)



### Definition

- characterized by pain and stiffness of the proximal extremities (girdle area)
- closely related to giant cell arteritis (15% of patients with PMR develop GCA)
- no muscle weakness

**Table 30. PMR Classification Criteria Scoring Algorithm****Required criteria: age  $\geq 50$ , bilateral shoulder aching, and abnormal ESR/CRP**

	Points without U/S (0-6)	Points with Abnormal U/S* (0-8)
Morning stiffness duration $>45$ min	2	2
Hip pain or limited ROM	1	1
Absence of RF or ACPA	2	2
Absence of other joint involvement	1	1
At least one shoulder with subdeltoid and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis on U/S	N/A	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or gleno-humeral synovitis on U/S	N/A	1

Ann Rheum Dis 2012;71:484-492

\*\*A score of 4 or more is categorized as PMR in the algorithm without U/S and a score of 5 or more is categorized as PMR in the algorithm with U/S

\*\*Optional U/S criteria

**Epidemiology**

- incidence 50 per 100,000 per year in those over age 50
- age of onset typically  $>50$ , F:M = 2:1

**Signs and Symptoms**

- constitutional symptoms prominent (fever, weight loss, malaise)
- pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs)
- gel phenomenon (stiffness after prolonged inactivity)
- physical examination reveals tender muscles, but no weakness or atrophy

**Investigations**

- bloodwork: often shows anemia, elevated platelets, elevated ESR and CRP; normal CK up to 5% of PMR reported with normal inflammatory markers

**Treatment**

- goal of therapy: symptom relief
- start with prednisone dose of 15-20 mg PO once daily
- taper slowly over 2-yr period monitoring ESR and symptoms closely
- treat relapses aggressively (50% relapse rate)
- monitor for steroid side effects, glucocorticoid-induced osteoporosis prevention, follow for symptoms of giant cell arteritis



Most patients are treated for up to 2 years.

**Prednisone Plus Methotrexate for PMR**

Ann Intern Med 2004;141:493-500

Study: Multicenter RCT.

Patients: Patients with newly diagnosed PMR.

Intervention: Prednisone dosage (25 mg/d) was tapered to 0 mg/d within 24 wk and was adjusted if flare-ups occurred. Oral methotrexate (10 mg) or placebo with folic acid supplementation (7.5 mg) was given weekly for 48 wk.

Primary Outcome: The proportion of patients no longer taking prednisone, the number of flare-ups, and the cumulative prednisone dose after 76 wk.

Results: 28 of 32 patients in the methotrexate group and 16 of 30 patients in the placebo group were no longer taking prednisone at 76 wk ( $p = 0.003$ ). Similar results were obtained after adjustment for C-reactive protein level and duration of symptoms in a multivariate model. 15 of 32 patients in the methotrexate group and 22 of 30 patients in the placebo group had at least 1 flare-up by the end of follow-up ( $p = 0.04$ ). The median prednisone dose was 2.1 g in the methotrexate group and 2.97 g in the placebo group ( $p = 0.03$ ). The rate and severity of adverse events were similar.

Limitations: Follow-up was short, and a high dose of folic acid and a relatively high starting dosage of prednisone were used. 10 of 72 patients (14%) discontinued treatment or were lost to follow-up.

Conclusions: Prednisone plus methotrexate is associated with shorter prednisone treatment and steroid sparing. It may be useful in patients at high risk for steroid-related toxicity.

## Fibromyalgia

**Definition**

- chronic ( $>3$  mo), widespread (axial, left- and right-sided, upper and lower segment), non-articular pain with characteristic tender points

**Diagnosis****2010 Diagnostic Criteria for Fibromyalgia**

- Widespread pain index (WPI)  $\geq 7$  and symptom severity score (SS)  $\geq 5$  or WPI 3-6 and SS  $\geq 9$
- Symptoms have been present at a similar level for  $\geq 3$  mo
- The patient does not have a disorder that would otherwise explain the pain
  - WPI = number of areas in which the patient had pain over the last week (L and R: shoulder girdle, upper arm, lower arm, hip, upper leg, lower leg, jaw, chest, abdomen, upper and lower back, neck = max score 19)
  - SS = sum of a) severity of fatigue, b) waking unrefreshed, and c) cognitive symptoms over the past week, plus d) extent of somatic symptoms (IBS, headache, abdominal pain/cramps, dry mouth, fever, hives, ringing in ears, vomiting, heartburn, dry eyes, SOB, loss of appetite, rash, hair loss, easy bruising, etc.); all (a-d) rated on 0-3 scale: 0=no problem, 1 = mild, 2 = moderate, 3 = severe
- this clinical definition identified 88.1% of ACR classified fibromyalgia and can allow longitudinal assessment of symptom severity

**Epidemiology**

- F:M = 3:1
- primarily ages 25-45, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness

## Signs and Symptoms

- widespread aching, stiffness
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent waking
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- neurologic symptoms of hyperalgesia, paresthesias
- associated with irritable bowel or bladder syndrome, migraines, tension headaches, restless legs syndrome, obesity, depression, and anxiety

## Investigations

- bloodwork: includes TSH and ESR; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

## Differential Diagnosis

- diagnosis of exclusion
- rule out other disorders by history and physical exam

## Treatment

- **conservative**
  - education
  - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
  - stress reduction, CBT
  - biofeedback, meditation, acupuncture may be helpful
- **medical**
  - low dose tricyclic antidepressant (e.g. amitriptyline)
    - ♦ for sleep restoration
    - ♦ select those with lower anticholinergic side effects
  - SNRI: duloxetine, milnacipran
  - anticonvulsant: pregabalin, gabapentin
  - analgesics may be beneficial for pain that interferes with sleep (NSAIDs, not narcotics)

## Prognosis

- variable; usually chronic, unless diagnosed and treated early

# Adult Onset Still's Disease

## Definition

- systemic inflammatory condition (ANA and RF negative) with fevers and characteristic rash, numerous systemic symptoms, may have severe arthritis

## Etiology and Pathophysiology

- idiopathic; infectious triggers likely – various viruses and bacteria have been implicated
- stress increases risk

## Epidemiology

- F>M; age of onset typically 16-40, approximately 1 per 100,000

## Signs and Symptoms

- classic triad of symptoms:
  - high-spiking fevers (95.7% of patients, typically T 39°C, <4 h duration, quotidian pattern)
  - characteristic "salmon rash" (~72% of patients, on proximal limbs + trunk)
  - arthralgia/arthritis (64-100%)
- sore throat, myalgias and serositis may also occur
- arthritis is symmetric, typically affects large joints, i.e. wrists, knees and ankles, may involve PIP and DIPs, elbow, MTPs
- liver abnormalities ± hepatomegaly (50-75% patients)
- splenomegaly (44%)



### A 14-week, RCT of Pregabalin in Patients with Fibromyalgia

*J Pain* 2008;9:792-880

**Study:** Multicenter RCT. 750 patients with fibromyalgia with pain score of <40 mm on the visual analog scale (VAS) were assigned to placebo or pregabalin (300 mg, 450 mg, or 600 mg) daily for 12 wk.

**Primary Outcome:** Change in the mean pain score derived from the subject's daily pain diary as measured at the patient's baseline to the end point of the study.

**Results:** Patients treated with 450 and 600 mg/d pregabalin showed a statistically significant improvement in the end point mean pain score compared with placebo-treated subjects by -0.50 and -0.45 respectively.

The 30% responder rate was 30%, 42%, 50%, and 48% in the placebo, 300 mg/d, 450 mg/d, and 600 mg/d respectively. The 50% responder rate was 15%, 24%, 27%, and 30% for placebo, 300 mg/d, 450 mg/d, and 600 mg/d respectively. Discontinuations due to adverse events were 12%, 16%, 22%, and 26% in placebo, 300 mg/d, 450 mg/d, and 600 mg/d respectively. The 450 and 600 mg/d groups were significantly different from placebo (P = .0001).

**Conclusions:** Pregabalin at 300 mg/d, 450 mg/d, and 600 mg/d showed statistically significant response rates as compared to placebo although discontinuation rates for the 450 mg/d and 600 mg/d regimens were significantly higher as compared to placebo.



### Exercise for Treating Fibromyalgia Syndrome

*Cochrane DB Syst Rev* 2008;CD003786

**Study:** Systemic review of exercise training including cardiorespiratory endurance, muscle strengthening, and flexibility for global well-being and physical function in patients with fibromyalgia.

**Result:** 34 studies were included (n=2276). Aerobic-only exercises improve global well-being, physical function, and possibly pain and tender points. There was insufficient data to evaluate the effect of strength and flexibility on the primary outcomes.

**Conclusions:** Moderate aerobic cardiorespiratory exercise improves function and well-being in patients with FM. Benefits from strength and flexibility require additional research to delineate benefits.



### Triad of Still's Disease

**FAR**

Fever

Arthralgias/Arthritis

Rash

### Classification

- numerous classification systems proposed
- Yamaguchi's criteria (J Rheumatol 1992;19:424-30) need 5 criteria to diagnose Still's, at least 2 major
  - major criteria
    - ♦  $T > 39^{\circ}\text{C}$ , intermittent,  $>1$  wk
    - ♦ typical rash
    - ♦  $\text{WBC} > 10,000$  ( $>80\%$  granulocytes)
  - minor criteria
    - ♦ sore throat
    - ♦ lymphadenopathy  $\pm$  splenomegaly
    - ♦ abnormal transaminases
    - ♦ negative ANA and RF
  - exclusion criteria: infection, malignancy, rheumatic disease

### Investigations

- ANA and RF negative
- markedly elevated ESR, CRP, ferritin (typically  $>1000$  ng/mL,  $>2200$  pmol/L)
  - total ferritin  $>5$  times ULN = 80% sensitive, 41% specific
- anemia, thrombocytosis, leukocytosis may occur
- transaminases, LDH may be elevated

### Treatment

- 1st line therapy: methotrexate + low-dose glucocorticoids  $\pm$  NSAIDs
- 2nd line therapy: other DMARDs (i.e. hydroxychloroquine, azathioprine, anti-IL1 and IL6 agents)

## Common Medications

**Table 31. Common Medications for Osteoarthritis**

Class	Generic Drug Name	Trade Name	Dosing (PO)	Indications	Contraindications	Adverse Effects
<b>NSAIDs</b>						
	acetaminophen	Tylenol®	500 mg tid q4h (4 g daily max)	1st line		Hepatotoxicity Overdose Potentiates warfarin
	ECASA ibuprofen diclofenac diclofenac/misoprostol naproxen meloxicam	Entrophen® Advil®, Motrin® Voltaren® Arthrotec® Naprosyn®, Aleve® Mobicox®	325-975 mg qid 200-600 mg tid 25-50 mg tid 50-75/200 mg tid 125-500 mg bid 7.5-15 mg OD	2nd line	GI bleed Renal impairment Allergy to ASA, NSAIDs Pregnancy (T3)	Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome
<b>COX-2 INHIBITORS</b>						
	celecoxib	Celebrex®	200 mg OD	High risk for GI bleed: age $>65$ hx of GI bleed, PUD	Renal impairment Sulfa allergy (celecoxib) Cardiovascular disease	Delayed ulcer healing Renal/hepatic impairment Rash
<b>Other treatments</b>		<b>Comments</b>				
Combination analgesics (acetaminophen + codeine, acetaminophen + NSAIDs)		Enhanced short term effect compared to acetaminophen alone More adverse effects: sedation, constipation, nausea, GI upset				
Intra-articular corticosteroid injection		Short-term (weeks-months) decrease in pain and improvement in function Used for management of an intraarticular inflammatory process when infection has been ruled out				
Intra-articular hyaluronic acid q6mo		Used for mild-moderate OA of the knees, however little supporting evidence, and not considered to be effective Precaution with chicken/egg allergy				
Topical NSAIDs		1.5% wt/wt topical diclofenac (Pennsaid®) May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy				
Capsaicin cream		Mild decrease in pain				
Glucosamine sulfate $\pm$ chondroitin		Limited clinical studies No regulation by Health Canada				



Table 32. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

Generic Drug Name	Trade Name	Dosing	Contraindications	Adverse Effects
COMMONLY USED				
hydroxychloroquine \$	Plaquenil®	400 mg PO OD initially 200-400 mg PO OD maintenance (6.5 mg/kg ideal body weight per day)	Retinal disease, G6PD deficiency	GI symptoms, skin rash, macular damage, neuromyopathy Requires regular ophthalmological screening to monitor for retinopathy
sulfasalazine \$	Salazopyrim® Azulfidine® (US)	1000 mg PO bid-tid	Sulfa/ASA allergy, kidney disease, G6PD deficiency	GI symptoms, rash, headache, leukopenia
methotrexate \$	Rheumatrex® Folex/Mexate®	7.5-25 mg PO/IM/SC qweekly	Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EtOH abuse	Oral ulcers, GI symptoms, cirrhosis, myelosuppression, pneumonitis, tubular necrosis
leflunomide \$\$	Arava®	10-20 mg PO OD	Liver disease	Alopecia, GI symptoms, liver dysfunction, pulmonary infiltrates
NOT COMMONLY USED				
cyclosporine \$\$	Neoral®	2.5-3 mg/kg/d divided and given in 2 doses PO	Kidney/liver disease, infection, hypertension	Hypertension, decreased renal function, hair growth, tremors, bleeding
gold (injectable) \$	Solganal® Mycrysine®	50 mg IM q1wk after gradual introduction	IBD, kidney/liver disease	Rash, mouth soreness/ulcers, proteinuria, marrow suppression
azathioprine \$	Imuran®	2/5 mg/kg/d PO once daily	Kidney/liver disease TPMT deficiency	Rash, pancytopenia (esp. ↓ WBC, ↑ AST, ALT), biliary stasis, vomiting, diarrhea
cyclophosphamide \$	Cytoxan®	1 g/m <sup>2</sup> /mo IV as per protocol	Kidney/liver disease	Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility
Generic Drug Name	Trade Name	Dosing	Mechanism of Action	
NEWER DMARDs (Biologics)				
etanercept \$\$\$	Enbrel®	25 mg biweekly or 50 mg weekly SC	Fusion protein of TNF receptor and Fc portion of IgG	
infliximab \$\$\$	Remicade®	3-5 mg/kg IV q8wk	Chimeric mouse/human monoclonal anti-TNF-α	
adalimumab \$\$\$	Humira®	40 mg SC q2wk	Monoclonal anti-TNF-α	
abatacept \$\$\$	Orencia®	IV infusion	Costimulation modulator of T-cell activation	
rituximab \$\$\$	Rituxan®	2 IV infusions, 2 wk apart	Causes B-cell depletion, binds to CD20	
certolizumab \$\$\$	Cimzia®	400 mg SC q2wk x3 then 200 mg SC q4wk	PEGylated monoclonal anti-TNF-α	
golimumab \$\$\$	Simponi®	50 mg SC q month	Monoclonal anti-TNF-α	
tocilizumab \$\$\$	Actemra®	4-8 mg/kg IV q4wk	Interleukin-6 receptor antagonist	

**Risks of Biologics:**

- Reactivation of TB or hepatitis B. Patients require negative TB skin test, chest x-ray and negative HBV serology prior to starting any of these medications
- Increased risk of serious infections
- Worsening heart failure

## Landmark Rheumatology Trials

Trial	Reference	Results
<b>RHEUMATOID ARTHRITIS</b>		
ATTEST	<i>Ann Rheum Dis</i> 2008; 67:1096-103	Abatacept and infliximab have similar efficacy in RA patients who have failed methotrexate
ATTRACT	<i>Lancet</i> 1999; 354:1932-9	Infliximab and methotrexate combined are more effective than methotrexate alone for patients with active RA
CIMESTRA	<i>Arthritis Rheum</i> 2006; 54:1401-9	Combination of methotrexate and sulfasalazine is superior to either alone
COMET	<i>Lancet</i> 2008; 372:375-82	Etanercept add-on therapy increases rates of remission in early RA
ERA	<i>NEJM</i> 2000; 343:1586-93	Etanercept more rapidly decreases symptoms in early RA compared to methotrexate
European Leflunomide Study Group	<i>Lancet</i> 1999; 353:259-66	Leflunomide is equal in efficacy to sulphasalazine
FIN-RACo	<i>Lancet</i> 1999; 353:1568-73	Combination therapy with DMARDs improves remission rates in early RA
Infliximab and methotrexate	<i>NEJM</i> 2000; 343:1594-602	Infliximab combined with methotrexate reduces joint damage in RA
Leflunomide Rheumatoid Arthritis Investigators Group	<i>Arch Intern Med</i> 1999; 159:2542-50	Leflunomide is equivalent to methotrexate therapy and superior to placebo
PREMIER	<i>Arthritis Rheum</i> 2006; 54:26-37	Combination therapy with adalimumab and methotrexate is superior to either alone in patients with early RA
Swefot	<i>Lancet</i> 2009; 374:459-66	Anti-TNF agents are more effective second-line therapy than DMARDs in patients who fail methotrexate
<b>OSTEOARTHRITIS</b>		
GAIT	<i>NEJM</i> 2006; 354:795-808	Glucosamine, chondroitin and the combination of both were no more effective than placebo in treatment of knee osteoarthritis
Hyaluronan	<i>Ann Rheum Dis</i> 2010; 69:1097-102	Hyaluronan injections do not improve disease activity in patients with moderate-severe knee OA
<b>LUPUS</b>		
Belimumab	<i>Lancet</i> 2011; 377:721-31	Treatment with belimumab reduces the incidence of BILAG A and B flares in patients with lupus compared to placebo
BILAG open-RCT	<i>Rheumatology</i> 2010; 49:723-32	Low dose cyclosporine and azathioprine are equivalent in efficacy as maintenance therapy for lupus
Mycophenylate mofetil or intravenous cyclophosphamide	<i>NEJM</i> 2005; 353:2219-28	Mycophenylate mofetil is more efficacious than cyclophosphamide in inducing remission of lupus nephritis
<b>CONNECTIVE TISSUE DISEASES</b>		
Azathioprine or methotrexate maintenance for ANCA-associated vasculitis	<i>NEJM</i> 2008; 359:2790-803	Methotrexate and azathioprine are equally safe and effective as maintenance agents in ANCA vasculitis
Cyclophosphamide in scleroderma lung disease	<i>NEJM</i> 2006; 354:2655-66	Cyclophosphamide therapy led to transient improvements in lung function, skin scores, and overall health in patients with scleroderma
Etanercept plus standard therapy for granulomatosis with polyangiitis	<i>NEJM</i> 2005; 352:351-61	Etanercept is not effective in inducing remission in patients with ANCA vasculitis
Mycophenylate mofetil vs. azathioprine for maintenance in ANCA-associated vasculitis	<i>JAMA</i> 2010; 304:2381-8	Mycophenylate mofetil is less effective than azathioprine at inducing remission in ANCA-associated vasculitis
Rituximab versus cyclophosphamide for ANCA-associated vasculitis.	<i>NEJM</i> 2010; 363:221-32	Rituximab is not inferior to cyclophosphamide for induction of maintenance in ANCA vasculitis
<b>GOUT</b>		
Febuxostat vs. allopurinol	<i>NEJM</i> 2005; 353:2450-61	Febuxostat is more effective than allopurinol at lowering serum urate, and has similar effectiveness on flare reduction

Trial	Reference	Results
<b>ANKYLOSING SPONDYLITIS</b>		
Adalimumab	<i>Arthritis Rheum</i> 2006; 54:2136-46	Adalimumab induced partial remission in 22% of AS patients
ATLAS (adalimumab)	<i>J Rheumatol</i> 2008; 35:1346-53	Compared to placebo, adalimumab significantly reduces pain and fatigue in AS patients
ASSERT (rituximab)	<i>Arthritis Rheum</i> 2005; 52:582-91	Sixty percent of patients treated with rituximab had a clinical response to the medication
Infliximab in AS	<i>Lancet</i> 2002; 359:1187-93	Infliximab induces regression of symptoms in 50% of patients and is superior to placebo
SPINE (etanercept)	<i>Ann Rheum Dis</i> 2011; 70:799-804	ETN has short-term efficacy for patients with advanced AS and reduces disease severity
Sulfasalazine	<i>Arthritis Rheum</i> 1995; 38:618-27	Sulfasalazine is superior to placebo in treatment of patients with seronegative spondyloarthropathy

## References

- ACR. Guidelines for the medical management of osteoarthritis of the hip. November 1995.
- ACR. Guidelines for the medical management of osteoarthritis of the knee. November 1995.
- ACR. Guidelines for referral and management of systemic lupus erythematosus in adults. Sept 1999.
- ACR Subcommittee on Rheumatoid Arthritis Guidelines, 2002. Guidelines for the management of rheumatoid arthritis, 2002 Update.
- Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria. *Arthritis and Rheumatism* 2010;62:2569-2581
- Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-324.
- American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002;46:328-346.
- Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *NEMJ* 2000;343:1586-1593.
- Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *NEMJ* 1975;292:403-407.
- Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. The VIGOR Study Group. *NEMJ* 2000;343:1520-1528.
- Bookman AM. Clinical evaluation of arthritis. University of Toronto foundations of medical practice lecture, 2006.
- Brady OH, Masri BA, Garbuz DS, Duncan CP. Joint replacement of the hip and knee – when to refer and what to expect. *CMAJ* 2000;163:1285-1291.
- Brater DC, Harris C, Redfern JS, Gertz BJ. Renal effects of COX-2-selective inhibitors. *Amer J Nephrol* 2001;21:1-15.
- CMAJ Clinical basics rheumatology series.
- Cibere J. Acute monoarthritis. *CMAJ* 2000;162:1577-1583.
- Clark BM. Physical and occupational therapy in the management of arthritis. *CMAJ* 2000;163:999-1005.
- Ensworth S. Is it arthritis? *CMAJ* 2000;162:1011-1016.
- Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. *Semin Arthritis Rheum* 1984;13:322-328.
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;40:1725.
- Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990;33:1122-1128.
- Huang SHK. Basics of therapy. *CMAJ* 2000;163:417-423
- Klippel JH, Weyand CM, Wortmann RL. Primer on Rheumatic Diseases, 11th ed. Arthritis Foundation, 1997.
- Klinckhoff A. Diagnosis and management of inflammatory polyarthritis. *CMAJ* 2000;162:1833-1838.
- Kremer, JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Ann Intern Med* 2001;134:695-706.
- Lacaille D. Advanced therapy. *CMAJ* 2000;163:721-728.
- Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum* 1990;33:1101-1017.
- Lightfoot RW Jr, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990;33:1088-1093.
- Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295-306.
- Musculoskeletal Injury; (OPOT). Queen's Printer of Ontario, June 2000. [www.opot.org](http://www.opot.org)
- Ontario Musculoskeletal Therapeutics Review Panel. Ontario treatment guidelines for osteoarthritis, rheumatoid arthritis, and acute price GE. Localized therapy. *CMAJ* 2000;163:176-183.
- Puttick MPE. Evaluation of the patient with pain all over. *CMAJ* 2001;164:223-227.
- Reid G, Esdaile JM. Getting the most out of radiology. *CMAJ* 2000;162:1318-1325.
- Shojania K. What laboratory tests are needed? *CMAJ* 2000;162:1157-1163.
- Smetana, GW, Shmerling RH. Does this patient have temporal arteritis? *JAMA* 2002;287:92-101.
- Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980;23:581-590.
- Taunton JE, Wilkinson M. Diagnosis and management of anterior knee pain. *CMAJ* 2001;164:1595-1601.
- Tsang I. Pain in the neck. *CMAJ* 2001;164:1182-1187.
- Van der Linden. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361.
- Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554-558.
- Wade, J.P. Osteoporosis. *CMAJ* 2001;165:45-50.
- Wing PC. Minimizing disability in patients with low-back pain. *CMAJ*. 2001;164:1459-1468.
- Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the multicenter criteria committee. *Arthritis Rheum* 1990;33:160-172.
- Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care and Research* 2010;62:600-610.

Alexandra L. Millman, Andrew Stewart and Clare Toguri, chapter editors

Jieun Kim and Daniel Soong, associate editors

Jeff Martin, EBM editor

Dr. Sender Herschorn and Dr. Armando Lorenzo, staff editors

<b>Acronyms</b> . . . . .	<b>2</b>	<b>Scrotal Mass.</b> . . . . .	<b>28</b>
<b>Basic Anatomy Review</b> . . . . .	<b>2</b>	<b>Penile Complaints</b> . . . . .	<b>29</b>
Abdominal Wall		Peyronie's Disease	
Anatomy of Scrotum		Priapism	
Genito-Urinary Tract Anatomy		Paraphimosis	
Penis Anatomy		Phimosis	
Male Pelvis and Perineum		Erectile Dysfunction (ED)	
		Premature Ejaculation	
<b>Urologic History</b> . . . . .	<b>3</b>	<b>Trauma</b> . . . . .	<b>32</b>
<b>Common Presenting Problems</b> . . . . .	<b>4</b>	Renal Trauma	
Macroscopic (Gross) Hematuria		Bladder Trauma	
Microscopic Hematuria		Urethral Injuries	
Dysuria		<b>Infertility</b> . . . . .	<b>34</b>
Hydronephrosis		Female Factors	
		Male Factors	
<b>Voiding Dysfunction</b> . . . . .	<b>6</b>	<b>Pediatric Urology</b> . . . . .	<b>36</b>
Voiding		Congenital Abnormalities	
Failure to Store: Urinary Incontinence		Nephroblastoma (Wilms' Tumour)	
Failure to Void: Urinary Retention		Cryptorchidism/Ectopic Testes	
Benign Prostatic Hyperplasia (BPH)		Disorders of Sexual Differentiation (DSD)	
Urethral Stricture		Circumcision	
Neurogenic Bladder		Enuresis	
Autonomic Dysreflexia			
Post Obstructive Diuresis (POD)		<b>Selected Urological Procedures</b> . . . . .	<b>41</b>
<b>Infectious and Inflammatory Diseases</b> . . . . .	<b>11</b>	Bladder Catheterization	
Urinary Tract Infection (UTI)		Cystoscopy	
Recurrent/Chronic Cystitis		Radical Prostatectomy	
Interstitial Cystitis (Painful Bladder Syndrome)		Transurethral Resection of the Prostate (TURP)	
Acute Pyelonephritis		Extracorporeal Shock Wave Lithotripsy (ESWL)	
Prostatitis/Prostatodynia			
Epididymitis and Orchitis		<b>Common Medications</b> . . . . .	<b>43</b>
Urethritis			
<b>Stone Disease</b> . . . . .	<b>16</b>	<b>References</b> . . . . .	<b>45</b>
Approach to Renal Stone			
<b>Urological Neoplasms</b> . . . . .	<b>19</b>		
Approach to Renal Mass			
Benign Renal Neoplasms			
Malignant Renal Neoplasms			
Carcinoma of the Renal Pelvis and Ureter			
Bladder Carcinoma			
Prostatic Carcinoma (CaP)			
CaP Screening			
Testicular Tumours			
Penile Tumours			

## Acronyms

$\beta$ -hCG	beta-human chorionic gonadotropin	ED	erectile dysfunction	Na <sup>+</sup>	sodium	SCC	squamous cell carcinoma
ABx	antibiotics	ESWL	extracorporeal shockwave lithotripsy	NaCl	sodium chloride	STI	sexually transmitted infection
AFP	alpha-fetoprotein	FNA	fine needle aspiration	NSGCT	non-seminomatous germ cell tumour	SUI	stress urinary incontinence
AST	assisted reproductive technologies	F/U	follow-up	OTC	over-the-counter	TCC	transitional cell carcinoma
AUA	American Urology Association	GA	general anesthesia	PCNL	percutaneous nephrolithotomy	TMP/SMX	trimethoprim/sulfamethoxazole
BPH	benign prostatic hyperplasia	HIFU	high-intensity focused ultrasound	PDE	phosphodiesterase	TRUS	transrectal ultrasound
CaP	prostatic carcinoma	HPF	high power field	PID	pelvic inflammatory disease	TUIP	transurethral incision of the prostate
CAH	congenital adrenal hyperplasia	HPTA	hypothalamic-pituitary-testicular axis	PMC	pontine micturition centre	TUNA	transurethral needle ablation
CBI	continuous bladder irrigation	Hx	history	POD	post-obstructive diuresis	TURBT	transurethral resection of bladder tumour
CF	cystic fibrosis	ICSI	intracytoplasmic sperm injection	PSA	prostate-specific antigen	TURP	transurethral resection of the prostate
CFU	colony-forming unit	IL-2	interleukin-2	PVD	peripheral vascular disease	U/A	urinalysis
CHF	congestive heart failure	IFN- $\alpha$	interferon-alpha	PUV	posterior urethral valve	U/O	urine output
CMG	cystometrogram	IPSS	International Prostate Symptom Score	PVR	post-void residual	U/S	ultrasound
CIC	clean intermittent catheterization	ISD	intrinsic sphincter deficiency	P/E	physical exam	UMN	upper motor neuron
CPSPS	chronic pelvic pain syndrome	IUI	intrauterine insemination	QOL	quality of life	UPJ	ureteropelvic junction
Cr	creatinine	IV	intravenous	RBC	red blood cell	URS	ureteroscopy
CVA	costovertebral angle	IVF	in vitro fertilization	RCC	renal cell carcinoma	UTI	urinary tract infection
CXR	chest x-ray	IVP	intravenous pyelogram	RFA	radio-frequency ablation	UVJ	ureterovesicular junction
C&S	culture and sensitivity	KUB	kidneys, ureters, bladder	RP	radical prostatectomy	VCUG	voiding cystourethrogram
D/C	discharge	LFT	liver function test	RPLND	retroperitoneal lymph node dissection	VIU	visual internal urethrotomy
DHT	dihydrotestosterone	LMN	lower motor neuron	RTA	renal tubular acidosis	VUR	vesicoureteral reflux
DM	diabetes mellitus	LUTS	lower urinary tract symptoms	RUG	retrograde urethrogram		
DRE	digital rectal exam	MET	medical expulsive therapy	R/O	rule out		
DSD	detrusor sphincter dyssynergia	MS	multiple sclerosis	SA	semen analysis		
EBRT	external beam radiation therapy						

## Basic Anatomy Review

- recall that the anatomical position of the penis is erect. Therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis.

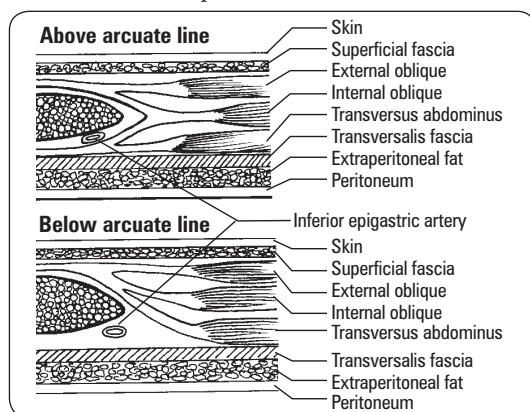


Figure 1. Midline cross-section of abdominal wall

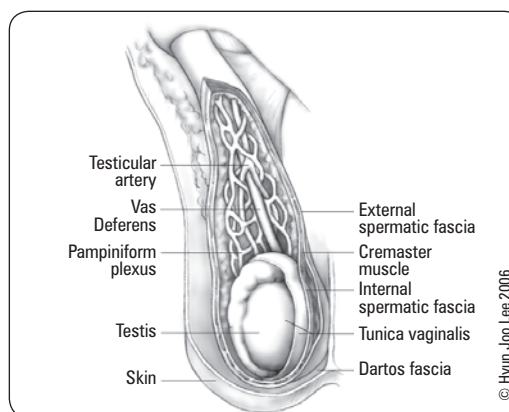


Figure 2. Anatomy of scrotum

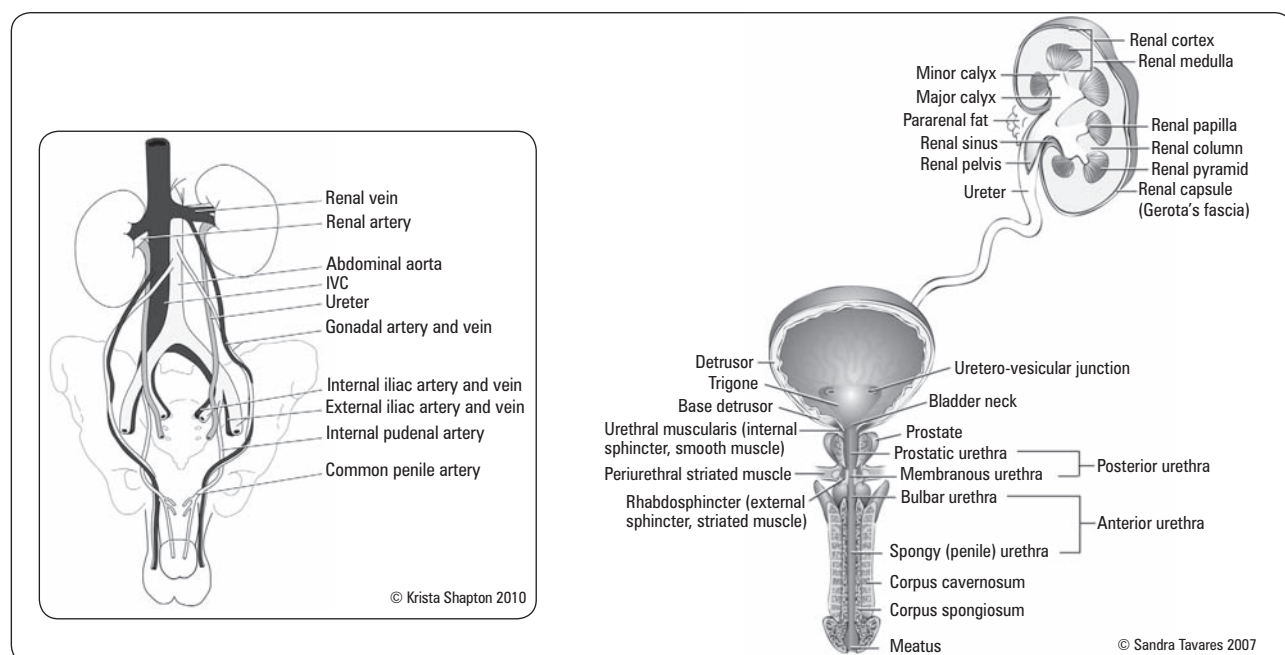


Figure 3. Essential genito-urinary tract anatomy

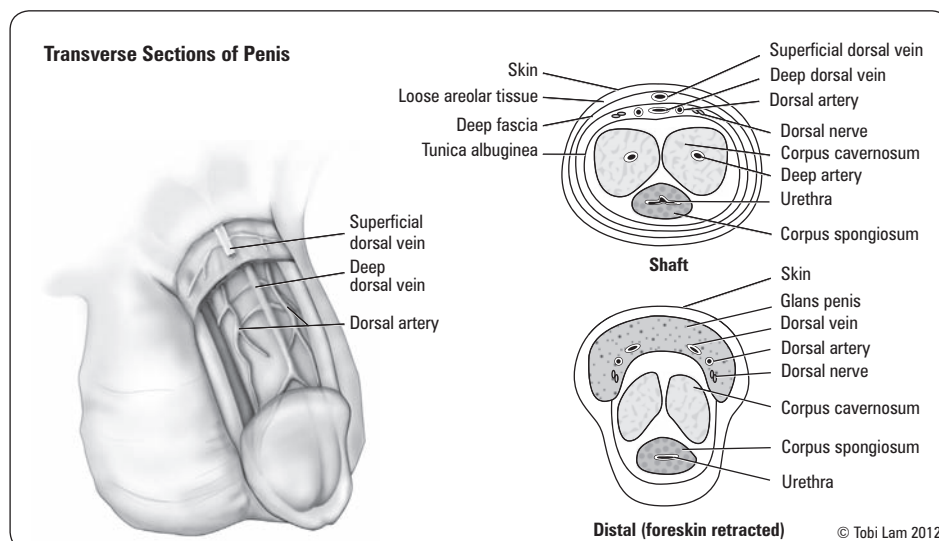


Figure 4. Cross section of the penis

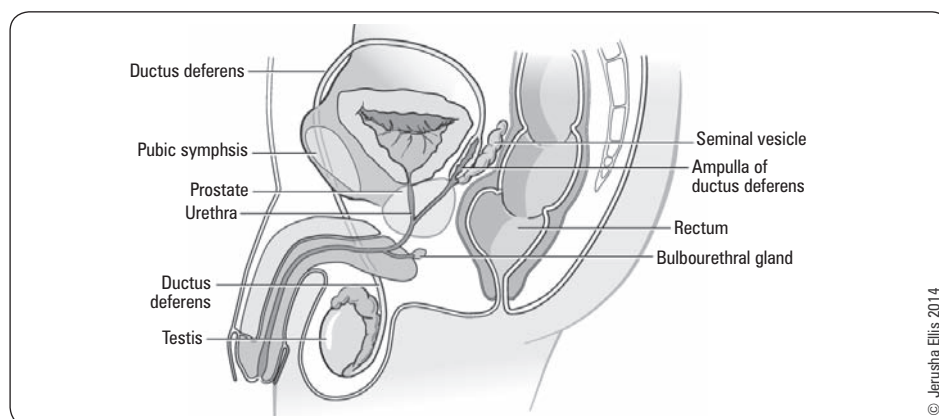


Figure 5. Median sagittal section of the male pelvis and perineum

## Urologic History

- follow the OPQRSTUVW approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
- inquire about risk factors: past urologic disease (e.g. UTI, stones, STI, cancers, anatomic abnormalities, family hx, medications, lifestyle factors, trauma, previous surgical procedures)
- constitutional symptoms: fever, chills, unintentional weight loss, night sweats, fatigue, malaise
- urinary output:
  - storage symptoms: frequency, nocturia, urgency, dysuria
  - voiding symptoms: straining, hesitancy, intermittency, post-void dribbling, reduced stream, feeling of incomplete voiding
  - hematuria: part of stream during which bleeding occurs, blood clots
  - incontinence: rushing to washroom (urge); leakage with coughing, sneezing, laughing (stress); constant dribbling (overflow)
- sexual function:
  - scrotal mass: see *Scrotal Mass*, U28
  - ED: see *Erectile Dysfunction*, U30
  - infertility: see *Infertility*, U34
- risk factors:
  - past urologic disease (e.g. UTI, stones, cancers, STI), anatomic abnormalities, trauma, previous surgical procedures, medications, family hx, lifestyle factors
- associated symptoms:
  - nausea/vomiting
- constitutional symptoms:
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise



Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant coronary artery disease. If there is new onset ED, ask about chest pain with exertion.



# Common Presenting Problems

## Macroscopic (Gross) Hematuria

### Definition

- blood in the urine that can be seen with the naked eye

**Classification** (see [Nephrology](#), NP21)

### Etiology

**Table 1. Etiology by Age Group**

Age (years)	Etiology
0-20	UTI, glomerulonephritis, congenital abnormalities
20-40	UTI, stones, bladder tumour
40-60	Male: bladder tumour, stones, UTI Female: UTI, stones, bladder tumour
>60	Male: BPH, bladder tumour, UTI, RCC Female: bladder tumour, UTI, RCC

**Table 2. Etiology by Type**

Pseudo-hematuria	Pre-renal	Renal	Post-renal
Vaginal bleeding	Anticoagulants	Trauma	BPH
Dyes (beets, rhodamine B in candy and juices)	Coagulation defects	RCC (mainly in adult population)	Stone
Hemoglobin (hemolytic anemia)	Sickle cell disease	TCC	Neoplasms
Myoglobin (rhabdomyolysis)	Leukemia	Wilms' tumour (mainly in pediatric population)	Cystitis
Drugs (rifampin, phenazopyridine, phenytoin)	Thromboembolism	Pyelonephritis	Urethritis
Porphyrria		Glomerulonephritis	Polyps
Laxatives (phenolphthalein)		Interstitial nephritis	Foreign body
		Tuberculosis	Urethral stricture
		Infarct	
		Polycystic kidneys	
		Arteriovenous malformation	
		Exercise-induced	

### History

- if macroscopic, inquire about timing of hematuria in urinary stream
  - initial: anterior urethra
  - terminal: bladder neck and prostatic urethra
  - total: bladder and/or above

### Investigations

- CBC (r/o anemia, leukocytosis), electrolytes, Cr, BUN
- urine studies:
  - U/A, C&S, cytology
- imaging:
  - CT (with contrast) has largely replaced IVP to investigate upper tracts (U/S alone is not sufficient)
  - cystoscopy to investigate lower tract (possible retrograde pyelogram)

### Acute Management of Severe Bladder Hemorrhage

- manual irrigation via catheter with normal saline to remove clots
- CBI using large (22-26 Fr) 3-way Foley to help prevent clot formation
- cystoscopy if active bleeding:
  - identify resectable tumours
  - coagulate obvious sites of bleeding
- refractory bleeding:
  - continuous intravesical irrigation with 1% aluminum potassium sulfate solution as needed
  - intravesical instillation of 1% silver nitrate solution
  - intravesical instillation of 1-4% formalin (requires GA and pre-procedure cystogram to r/o reflux)
  - embolization or ligation of iliac arteries
  - cystectomy and diversion (rarely performed)



Gross, painless hematuria in adults is bladder cancer until proven otherwise.



**Common Urologic Causes of Hematuria Can Be Classified As:**

#### TICS

Trauma/Tumour/Toxins  
Infection/Inflammatory  
Calculi/Cysts  
Surgery/Sickle cell and other hematological causes



#### Upper Tract Imaging Options

##### Intravenous Pyelogram (IVP):

Traditional option but rarely used (replaced by CTU). Reasonable sensitivity for TCC, but poor sensitivity for RCC.

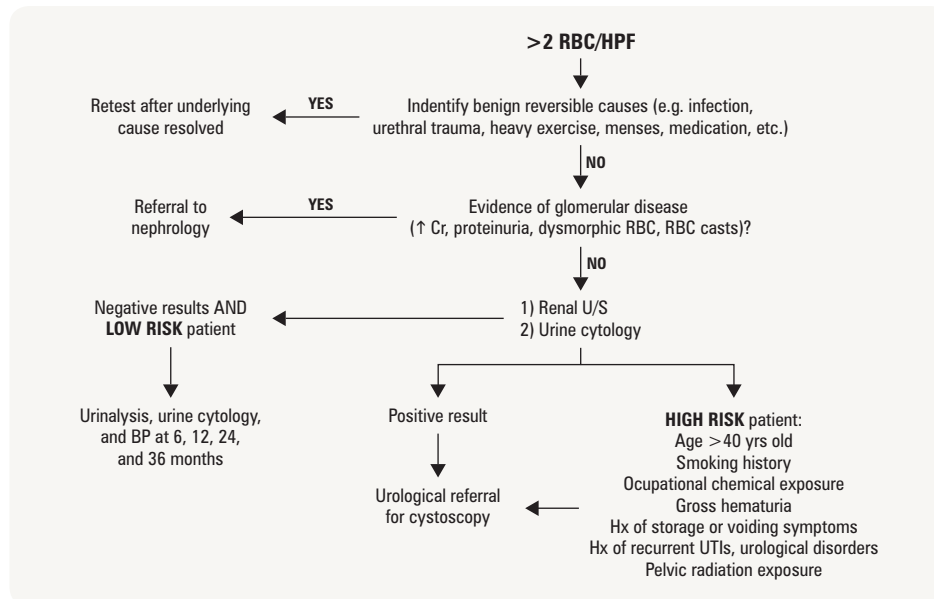
**U/S:** Superior to IVP for evaluation of renal parenchyma and renal cysts. Limited sensitivity for TCC and small renal masses. U/S alone is not sufficient for upper tract imaging.

**CT Urography (CTU):** Optimal test for renal parenchyma, calculi, and infections. Involves exposure to radiation and IV contrast. Assess kidney function prior to use of contrast.

## Microscopic Hematuria

### Definition

- >2 RBCs/HPF on urinalysis of two separate samples



**Figure 6. Workup of asymptomatic microscopic hematuria**

Based on CUA Guidelines. AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative work-up is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists

## Dysuria

### Definition

- painful urination

### Etiology

**Table 3. Differential Diagnosis of Dysuria**

<b>Infectious</b>	Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perineal inflammation/infection, TB, vestibulitis
<b>Neoplasm</b>	Kidney, bladder, prostate, penis, vagina/vulva, BPH
<b>Calculi</b>	Bladder stone, ureteral stone, kidney stone
<b>Inflammatory</b>	Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis
<b>Hormonal</b>	Endometriosis, hypoestrogenism
<b>Trauma</b>	Catheter insertion, post-coital cystitis (honeymoon cystitis)
<b>Psychogenic</b>	Somatization disorder, depression, stress/anxiety disorder
<b>Other</b>	Contact sensitivity, foreign body, radiation/chemical cystitis

### Investigations

- focused hx and P/E to determine cause (fever, D/C, conjunctivitis, CVA tenderness, back/joint pain)
  - any D/C (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal D/C
  - U/A and urine C&S
  - if suspect infection, may start empiric ABx treatment (see Table 8 in *Infectious and Inflammatory Disease*, U11, for ABx)
  - ± imaging of urinary tract (tumour, stones)

## Hydronephrosis

### Definition

- dilation of the renal pelvis and calyces caused by the backward pressure of trapped urine

### Etiology

- mechanical:
  - congenital: see *Congenital Abnormalities*, U36
  - acquired:
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral stricture, phimosis
    - extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
- functional:
  - neurogenic: neurogenic bladder, diabetic neuropathy, spinal cord disease
  - pharmacologic: anticholinergics,  $\alpha$ -adrenergic agonists
  - hormonal: pregnancy (progesterone decreases ureteral tone)

### Investigations

- focused hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, hx of UTIs, calculi and PID
- CBC, electrolytes, Cr, BUN, U/A, C&S
- imaging studies (U/S is >90% sensitive and specific)

### Treatment

- aimed at relieving the cause of obstruction/stasis
- urgent treatment is required if associated with infection, acute renal failure, or severe pain
  - percutaneous nephrostomy tube or ureteral stenting to relieve pressure

## Voiding Dysfunction

- see [Gynecology](#), GY34 for relevant female topics



## Voiding

- two phases of lower urinary tract function:
  - storage phase (bladder filling and urine storage):
    - accommodation and compliance
    - no involuntary contraction
  - voiding phase (bladder emptying):
    - coordinated detrusor contraction
    - synchronous relaxation of outlet sphincters
    - no anatomic obstruction
- voiding dysfunction can therefore be classified as:
  - failure to store: due to bladder or outlet
  - failure to void: due to bladder or outlet
- three types of symptoms
  - storage (formerly known as irritative)
  - voiding (formerly known as obstructive)
  - post-voiding

## Failure to Store: Urinary Incontinence

### Definition

- involuntary leakage of urine

### Etiology

- urgency incontinence:
  - detrusor overactivity:
    - CNS lesion, inflammation/infection (cystitis, stone, tumour), bladder neck obstruction (tumour, stone), BPH, idiopathic
  - decreased compliance of bladder wall:
    - CNS lesion, fibrosis
    - sphincter/urethral problem



#### Lower Urinary Tract Symptoms (LUTS)

##### Storage (FUND)

Frequency  
Urgency  
Nocturia  
Dysuria

##### Voiding (SHED)

Stream changes  
Hesitancy  
Incomplete Emptying  
Dribbling

- stress urinary incontinence (SUI):
  - common in women; seen in men after prostate cancer treatment or pelvic operations
  - urethral hypermobility:
    - ♦ weakened pelvic floor and musculofascial urethral and vaginal supporting mechanisms allows bladder neck and urethra to descend with increased intra-abdominal pressure
    - ♦ urethra is pulled open by greater motion of posterior wall of outlet relative to anterior wall
    - ♦ associated with childbirth, pelvic surgery, aging, levator muscle weakness
  - intrinsic sphincter deficiency (ISD): weakness of the urethra and associated smooth and striated muscle elements
    - ♦ pelvic surgery, neurologic problem, aging and hypoestrogen state
  - ISD and urethral hypermobility can co-exist
- mixed incontinence:
  - combination of stress and urgency incontinence
- overflow incontinence:
  - is a term sometimes used to describe urinary incontinence as a complication of urinary retention; for causes of urinary retention see *Failure to Void: Urinary Retention*, below
  - the International Continence Society no longer recommends the use of this term as it is confusing and lacks a clear definition; if the term is used it should be accompanied by the associated pathophysiology (e.g. BPH with overflow incontinence)

### Epidemiology

- variable prevalence in women: 25-45%
- F:M = 2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

**Table 4. Urinary Incontinence: Types and Treatments**

Type	Urgency	Stress	Mixed
<b>Definition</b>	Involuntary leakage of urine preceded by a strong, sudden urge to void	Involuntary leakage of urine with sudden increases in intra-abdominal pressure	Urinary leakage associated with urgency and increased intra-abdominal pressure
<b>Etiology</b>	Bladder (detrusor overactivity)	Urethra/sphincter weakness, post-partum pelvic musculature weakness	Combination of bladder and sphincter issues
<b>Diagnosis</b>	Hx Urodynamics	Hx Urodynamics Stress test (have patient bear down/cough)	Hx Stress test
<b>Therapy</b>	Anticholinergics Lifestyle changes (fluid alterations, diet, etc.) Bladder habit training Botulinum toxin Neuromodulation	Weight loss Kegel exercises Bulking agents Surgery (slings, tension-free vaginal tape, transobturator tape, artificial sphincters)	Combination of management of urge and stress incontinence



#### Causes of Reversible Urinary Incontinence

##### DIAPERS

Delirium

Inflammation/Infection

Atrophic vaginitis/urethritis

Pharmaceuticals/Psychological

Excess U/O

Restricted mobility/Retention

Stool impaction



Urgency is the symptom of a strong need to void. It is not necessarily associated with incontinence.

## Failure to Void: Urinary Retention

**Table 5. Etiology of Urinary Retention**

Outflow Obstruction	Bladder Innervation	Pharmacologic	Infection
<ul style="list-style-type: none"> <li>• Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurological (DSD)</li> <li>• Prostate: BPH, prostate cancer</li> <li>• Urethra: stricture, phimosis, traumatic disruption</li> <li>• Miscellaneous: constipation, pelvic mass</li> </ul>	<ul style="list-style-type: none"> <li>• Intracranial: CVA, tumour, Parkinson's, cerebral palsy</li> <li>• Spinal cord: injury, disc herniation, MS</li> <li>• DM</li> <li>• Post-abdominal or pelvic surgery</li> </ul>	<ul style="list-style-type: none"> <li>• Anticholinergics</li> <li>• Narcotics</li> <li>• Antihypertensives (ganglionic blockers, methyldopa)</li> <li>• OTC cold medications containing ephedrine or pseudoephedrine</li> <li>• Antihistamines</li> <li>• Psychosomatic substances (e.g. ecstasy)</li> </ul>	<ul style="list-style-type: none"> <li>• GU: UTI, prostatitis, abscess, genital herpes</li> <li>• Infected foreign body</li> <li>• Varicella zoster</li> </ul>

### Clinical Features

- suprapubic pain
- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal D/C
- increased size of prostate or reduced anal sphincter tone on DRE
- neurological: presence of abnormal or absent deep tendon reflexes, reduced "anal wink", saddle anesthesia



#### Acute vs. Chronic Retention

Acute retention is a medical emergency characterized by pain and anuria with normal bladder volume and architecture. Acute overdistention can lead to bladder rupture.

Chronic retention can be asymptomatic with greatly increased bladder volume and detrusor hypertrophy followed by atony (late).



If a trauma patient is unable to void, has blood at urethral meatus, a scrotal hematoma, or a high riding prostate, there is urethral injury until proven otherwise so catheterization is CONTRAINDICATED unless performed by urology staff or resident.

## Investigations

- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

## Treatment

- treat underlying cause
- catheterization:
  - acute retention
    - ♦ immediate catheterization to relieve retention; leave Foley in to drain bladder; F/U to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - ♦ intermittent catheterization by patient is commonly used; definitive treatment depends on etiology
- suprapubic tube placement
- for post-operative patients with retention:
  - encourage ambulation
  - $\alpha$ -blockers to relax bladder neck outlet
  - may need catheterization
  - definitive treatment will depend on etiology



Patients with ascites may have a falsely elevated PVR measured by bladder scan.

## Benign Prostatic Hyperplasia (BPH)

### Definition

- periurethral hyperplasia of stroma and epithelium in prostatic transition zone (see Figure 7)
- prostatic smooth muscle cells play a role in addition to hyperplasia

### Etiology

- etiology unknown
  - DHT required (converted from testosterone by 5- $\alpha$  reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors

### Epidemiology

- age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
- 25% of men will require treatment

### Clinical Features

- result from outlet obstruction and compensatory changes in detrusor function
- voiding symptoms:
  - hesitancy, straining, weak/interrupted stream, incomplete bladder emptying
- storage symptoms:
  - urgency, frequency, nocturia, urgency incontinence
  - thought to be due to detrusor overactivity and/or decreased compliance
- DRE
  - prostate is smooth, rubbery and symmetrically enlarged
- complications:
  - retention
  - overflow incontinence
  - hydronephrosis
  - infection
  - gross hematuria
  - bladder stones

### Investigations

- hx, assessing LUTS and impact on QOL
  - may include self-administered questionnaires (IPSS or AUA symptom index for severity, progression, and treatment response)
- P/E, including DRE
- U/A to exclude UTI
- Cr  $\pm$  renal U/S to assess for hydronephrosis
- PSA to r/o malignancy (see *CaP Screening*, U25)
- uroflowmetry to measure flow rate (optional)
- PVR (optional)
- cystoscopy prior to potential surgical management
- biopsy if suspicious for malignancy

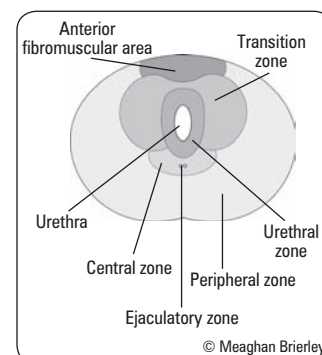


Figure 7. Cross-section of prostate



Prostate size does not correlate well with symptoms in BPH.



### Approximate Prostate Sizes

- 20 cc – chestnut
- 25 cc – plum
- 50 cc – lemon
- 75 cc – orange
- 100 cc – grapefruit



### AUA Prostate Symptom Score

#### FUNWISE

Frequency  
Urgency  
Nocturia  
Weak stream  
Intermittency  
Straining  
Emptying, incomplete feeling of

Each symptom graded out of 5  
0-7: Mildly symptomatic  
8-19: Moderately symptomatic  
20-35: Severely symptomatic

Note: dysuria not included in score but is commonly associated with BPH

## Treatment

**Table 6. Treatment of BPH**

	Conservative	Medical	Surgical	Minimally Invasive Surgical Therapies
<b>When to use</b>	All patients	Moderate to severe symptoms	Moderate to severe symptoms	Patients who wish to avoid or may not tolerate surgery
<b>Options</b>	<ul style="list-style-type: none"> <li>• Watchful waiting: 50% of patients improve spontaneously</li> <li>• Lifestyle modifications (e.g. evening fluid restriction, planned voiding)</li> </ul>	<ul style="list-style-type: none"> <li>• <math>\alpha</math>-adrenergic antagonists: reduce stromal smooth muscle tone</li> <li>• 5-<math>\alpha</math> reductase inhibitor: block conversion of testosterone to DHT; act to reduce prostate size</li> <li>• Combination is synergistic</li> <li>• Anti-cholinergic agents (for storage LUTS, without elevated PVR)</li> </ul>	<ul style="list-style-type: none"> <li>• TURP (see U42)</li> <li>• Laser ablation</li> <li>• TUIP (prostate &lt;30 g)</li> <li>• Open prostatectomy</li> </ul>	<ul style="list-style-type: none"> <li>• Microwave therapy</li> <li>• TUNA</li> <li>• Prostatic stent</li> </ul>



Men with planned cataract surgery should avoid starting  $\alpha$ -adrenergic antagonists until after their surgery due to the risk of intraoperative floppy iris syndrome.



**BPH Surgery**  
**Absolute Indication**

- Renal failure with obstructive uropathy
- Refractory urinary retention

**Relative Indications**

- Recurrent UTIs
- Recurrent hematuria refractory to medical treatment
- Renal insufficiency (r/o other causes)
- Bladder stones

## Urethral Stricture



### Definition

- decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

### Etiology

- congenital
  - failure of normal canalization (technically not a stricture)
- trauma:
  - instrumentation/catheterization (most common)
  - external trauma (e.g. burns, straddle injury)
  - foreign body
- infection:
  - long-term indwelling catheter
  - STI
- inflammation:
  - balanitis xerotica obliterans (lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal stenosis

### Clinical Features

- voiding symptoms
- urinary retention
- hydronephrosis
- related infections: recurrent UTI, secondary prostatitis/epididymitis

### Investigations

- laboratory findings
  - flow rates <10 mL/s (normal ~20 mL/s) on uroflowmetry
  - urine culture usually negative, but U/A may show pyuria
- radiologic findings
  - RUG and VCUG will demonstrate location
- cystoscopy

### Treatment

- urethral dilatation:
  - temporarily increases lumen size by breaking up scar tissue
  - healing will often reform scar tissue and recreate stricture
- visual internal urethrotomy (VIU):
  - endoscopically incise stricture
  - cure rate 50-80% with single treatment, <50% with repeated courses
- open surgical reconstruction:
  - complete stricture excision with anastomosis,  $\pm$  urethroplasty depending on location and size of stricture



**The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia Medical Therapy of Prostatic Symptoms (MTOPS) Trial**

*NEJM* 2003;349:2387-2398

**Study:** Randomized, double-blinded, controlled trial with mean follow-up of 4.5 yr.

**Methods:** 3047 patients with symptomatic BPH were randomly assigned to placebo (n=737), doxazosin (n=756), finasteride (n=768), or combination therapy (n=786). Mean age 62.6. Interventions that were compared were conservative treatment vs. doxazosin vs. finasteride vs. combination therapy. Main outcomes were clinical progression defined as: first occurrence of an increase over base line of at least four points in the AUA symptom score, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence.

**Results:** The 6-yr absolute reduction in cumulative incidence of clinical progression of symptomatic BPH compared to placebo for doxazosin was 39% (P<0.001), finasteride was 34% (P=0.002), and combination therapy was 66% (P<0.001). Combination therapy was more effective than either doxazosin (P<0.001) or finasteride (P<0.001) alone. There was no significant difference between doxazosin and finasteride alone.

**Conclusion:** Long-term combination therapy with doxazosin and finasteride reduced the risk of overall clinical progression of benign prostatic hyperplasia significantly more than did treatment with either drug alone.



## Neurogenic Bladder

### Definition

- malfunctioning urinary bladder due to deficiency in some aspect of its innervation

### Neurophysiology

**Table 7. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply**

Nerve Fibres	Nerve Roots	Neurotransmitter/Receptor	Target
Sympathetic T10-L2	T10-L2	NA/Adrenergic	Trigone, internal sphincter, proximal urethra Bladder body
Somatic (pudendal)	S2-4	ACh/Nicotinic	External sphincter
Parasympathetic	S2-4	ACh/Muscarinic (M2, M3)	Detrusor

- stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  - micturition:
    - stimulation of parasympathetic neurons (bladder contraction)
    - inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  - urine storage:
    - opposite of micturition
- voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
- cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem

### Classification of Neurologic Voiding Dysfunction

- neurogenic detrusor overactivity (formerly termed detrusor hyperreflexia):
  - lesion above PMC (e.g. stroke, tumour, MS, Parkinson's disease)
  - loss of voluntary inhibition of voiding
  - intact pathway inferior to PMC maintains coordination of bladder and sphincter
- detrusor sphincter dyssynergia (DSD):
  - lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  - loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  - component of detrusor overactivity as well
- detrusor atony/areflexia:
  - lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality)
  - flaccid bladder which fails to contract
  - may progress to poorly compliant bladder with high pressures
- peripheral autonomic neuropathy:
  - deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
- muscular lesion:
  - can involve detrusor, smooth/striated sphincter

### Neuro-Urologic Evaluation

- hx and P/E (urologic and general neurologic)
- U/A, renal profile
- imaging
  - IVP (less used), U/S to r/o hydronephrosis and stones
- cystoscopy
- urodynamic studies:
  - uroflowmetry to assess flow rate, pattern
  - filling CMG to assess capacity, compliance, detrusor overactivity
  - voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
  - video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
  - EMG ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

### Treatment

- goals of treatment:
  - prevent renal failure
  - prevent infections
  - achieve social continence



#### 4Cs of Bladder

Capacity: 350-500 cc;  
 peds: (age in yrs + 2) x 30  
 Compliance: minimal  
 $\Delta$  Pressure/ $\Delta$  Volume  
 Contractility: voluntary and sustained  
 Cooperation: of bladder and sphincter



Nerve roots in micturition:

**"S2-3-4 keeps the urine off the floor."**



**"Spinal shock"**, initially manifests as atonic bladder.

- treatment options depend on status of bladder and urethra
  - bladder hyperactivity → medications to relax bladder (see *Urinary Incontinence*, U6)
    - ♦ if refractory:
      - botulinum toxin injections into bladder wall
      - occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      - occasionally urinary diversion (ileal conduit or continent diversion) if bladder management unsuccessful
  - flaccid bladder → CIC

## Autonomic Dysreflexia

- occurs in patients with spinal cord injury above T6/T7
- exaggerated sympathetic nervous system response to visceral stimulation below the lesion
  - stimulation includes instrumentation or distension of bladder, urethra, or rectum
- symptoms include HTN, headache, reflex bradycardia, sweating, anxiety, piloerection
  - vasoconstriction below lesion, vasodilation above lesion
- treatment: removal of noxious stimuli, parenteral ganglionic or  $\alpha$ -blockers, nifedipine (prophylaxis during cystoscopy)

## Post-Obstructive Diuresis (POD)

### Definition

- polyuria resulting from relief of severe chronic obstruction
- $>3$  L/24 h or  $>200$  cc/h over each of two consecutive hours

### Pathophysiology

- **physiologic POD** secondary to excretion of retained urea,  $\text{Na}^+$ , and  $\text{H}_2\text{O}$  (high osmotic load) after relief of obstruction
  - self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
- **pathologic POD** is a  $\text{Na}^+$ -wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to:
  - decreased reabsorption of  $\text{NaCl}$  in the thick ascending limb and urea in the collecting tubule
  - increased medullary blood flow (solute washout)
  - increased flow and solute concentration in the distal nephrons

### Management

- admit patient and closely monitor hemodynamic status and electrolytes ( $\text{Na}^+$  and  $\text{K}^+$  q6-12h and replace prn; follow Cr and BUN to baseline)
- monitor U/O q2h and ensure total fluid intake  $<$ U/O by replacing every 1 cc U/O with 0.5 cc 1/2 NS IV (PO fluids if physiologic POD)
- avoid glucose-containing fluid replacement (iatrogenic diuresis)

## Infectious and Inflammatory Diseases

Table 8. Antibiotic Treatment of Urological Infections

Condition	Drug	Duration
Urethritis	non-gonococcal:	
	azithromycin (1 g PO)	x 1
	OR	
	doxycycline (100 mg PO bid)	7 d
	gonococcal:	
	ceftriaxone (250 mg IM) AND treat for <i>Chlamydia trachomatis</i>	x 1
Simple, Uncomplicated UTI	TMP-SMX (160 mg/800 mg PO bid)	3 d
	OR	
	nitrofurantoin (100 mg PO bid)	5 d
Complicated UTI (see <i>Classification</i> for features)	ciprofloxacin (1 g PO daily OR 400 mg IV q12h)	up to 2-3 wk
	OR	
	ampicillin (1 g IV q6h) + gentamicin (1 mg/kg IV q8h)	up to 2-3 wk
	OR	
	ceftriaxone (1-2 g IV q24h)	up to 2-3 wk
Recurrent/Chronic Cystitis	*prophylactic treatment	
	continuous: TMP-SMX (40 mg/200 mg PO qd OR 3x/wk)	6-12 mo
	post-coital: TMP-SMX (40 mg/200 mg-80 mg/400 mg)	within 2 h of coitus



Uncomplicated UTI in men  $<50$  should be treated with 7 d courses of TMP-SMX.

**Table 8. Antibiotic Treatment of Urological Infections** (continued)

Condition	Drug	Duration
<b>Acute Prostatitis</b>	ciprofloxacin (500-750 mg PO bid)	2-4 wk
	OR	
	TMP-SMX (160 mg/800 mg PO bid)	4 wk
	OR	
	IV therapy with gentamicin and ampicillin, penicillin w/ $\beta$ -lactamase inhibitor, 3 <sup>rd</sup> gen cephalosporin, OR a fluoroquinolone	4 wk total (IV and oral step-down)
<b>Chronic Prostatitis</b>	ciprofloxacin (500 mg PO bid)	4-6 wk
<b>Epididymitis/Orchitis</b>	<35 yr:	
	ceftriaxone (200 mg IM)	x 1
	AND	
	doxycycline (100 mg PO bid)	10 d
	$\geq 35$ yr:	
	ofloxacin (300 mg PO bid)	10 d
<b>Acute Uncomplicated Pyelonephritis</b>	ciprofloxacin (500 mg PO bid)	7 d
	$\pm$ ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV)	x 1
	OR	
	IV therapy with a fluoroquinolone, gentamicin and ampicillin, extended spectrum cephalosporin, extended spectrum penicillin, OR a carbapenem	14 d total (IV and oral step-down)



Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results.



IV antibiotics should be stepped down to oral when the patient is afebrile and clinically stable.



Acute uncomplicated pyelonephritis: suspected or confirmed enterococcus infection requires treatment with ampicillin.

## Urinary Tract Infection (UTI)

- for UTIs during pregnancy, see [Obstetrics](#), OB20

### Definition

- symptoms suggestive of UTI (see *Clinical Features* below) + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy)

### Classification

- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, immunocompromised, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see *Recurrent/Chronic Cystitis*, U13

### Risk Factors

- stasis and obstruction:
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder
- foreign body:
  - introduce pathogen or act as nidus of infection e.g. catheter, instrumentation
- decreased resistance to organisms:
  - DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors:
  - trauma, anatomic abnormalities, female, sexual activity, fecal incontinence

### Clinical Features

- storage symptoms: frequency, urgency, dysuria
- voiding symptoms: hesitancy, post-void dribbling
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

### Organisms

- typical organisms (see sidebar)
- atypical organisms:
  - tuberculosis (TB)
  - Chlamydia trachomatis*
  - Mycoplasma (*Ureaplasma urealyticum*)
  - fungi (*Candida*)

### Indications for Investigations

- pyelonephritis
- persistence of pyuria/symptoms following adequate therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- hx of structural abnormalities/decreased flow



#### Cystitis: Common Pathogens

##### KEEPS

*Klebsiella* sp.  
*E. coli* (90%), other Gram-negatives  
*Enterococci*  
*Proteus mirabilis*, *Pseudomonas*  
*S. saprophyticus*

**Investigations**

- U/A, urine C&S
  - UA: leukocytes  $\pm$  nitrites  $\pm$  hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see *Microscopic Hematuria*, U5)
- CT scan if indicated

**Treatment**

- see Table 8 for approach to ABx therapy
- if febrile, consider admission with IV therapy and r/o obstruction

## Recurrent/Chronic Cystitis

**Definition**

- $\geq 3$  UTIs/12 mo

**Etiology**

- bacterial reinfection (80%) vs bacterial persistence (relapse)
  - **bacterial reinfection:**
    - ♦ recurrence of infection with either 1) a different organism, 2) the same organism if cultured  $>2$  wk following therapy, or 3) with any organism with an intermittent sterile culture
  - **bacterial persistence:**
    - ♦ same organism cultured within 2 wk of sensitivity-based therapy

**Investigations**

- assess predisposing factors as described above
- investigations may include cystoscopy, U/S, CT

**Treatment**

- lifestyle changes (limit caffeine intake, increase fluid/H<sub>2</sub>O intake)
- ABx: continuous vs. post-coital (see Table 8)
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

**Prevention of UTIs**

- Maintain good hydration (especially with cranberry juice)
- Wipe from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

## Interstitial Cystitis (Painful Bladder or Bladder Pain Syndrome)

**Definition**

- chronic urgency, frequency  $\pm$  pain without other reasonable causation

**Classification**

- non-ulcerative (more common)
- ulcerative

**Etiology**

- unknown
  - theories: increased epithelial permeability, autoimmune, neurogenic, defective glycosaminoglycan (GAG) layer overlying mucosa
  - associations: severe allergies, IBS, fibromyalgia

**Epidemiology**

- prevalence: 20/100,000
- 90% of cases are in females
- mean age at onset is 40 yr (non-ulcerative tends to affect a younger to middle-aged population, while ulcerative tends to be seen in middle-aged to older)

**Clinical Features**

- pain associated with the bladder
- glomerulations (submucosal petechiae) or Hunner's ulcers on cystoscopic examination
- urinary urgency
- negative U/A, urine C&S, and urine cytology

**Differential Diagnosis**

- UTI, vaginitis, bladder tumour
- radiation/chemical cystitis
- eosinophilic/TB cystitis
- bladder calculi



Cystoscopic evaluation is not necessary to make a diagnosis.

**Treatment**

- first-line: patient empowerment (diet, lifestyle, stress management), pain management
- second-line:
  - oral: pentosan polysulfate sodium, amitriptyline, cimetidine, hydroxyzine
  - intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine
- third-line: cystoscopy with bladder hydrodistention (traditionally diagnostic) under GA, treat Hunner's ulcers if present
- other: neuromodulation, cyclosporine A, intradetrusor botulinum toxin
- surgery (last resort): augmentation cystoplasty, or urinary diversion ± cystectomy



Four symptom scores exist to evaluate and monitor patients with interstitial cystitis:

- Interstitial Cystitis Symptom Index (ICSI)
- Interstitial Cystitis Problem Index (ICPI)
- Wisconsin Interstitial Cystitis (UW-IC) Scale
- Pain, Urgency and Frequency (PUF) Score

## Acute Pyelonephritis

**Definition**

- infection of the renal parenchyma with local and systemic manifestations

**Etiology**

- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
- causative microorganisms:
  - gram positives: *Enterococcus faecalis*, *S. aureus*, *S. saprophyticus*
  - gram negatives: *E. coli* (most common), *Klebsiella*, *Proteus*, *Pseudomonas*, *Enterobacter*
- common underlying causes of pyelonephritis
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

**Clinical Features**

- rapid onset (<24 h)
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness or exquisite flank pain

**Investigations**

- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging indicated if suspicious of complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

**Treatment**

- hemodynamically stable:
  - outpatient oral ABx treatment ± single initial IV dose (see Table 8)
- severe or non-resolving:
  - admit, hydrate, and treat with IV ABx (see Table 8)
- emphysematous pyelonephritis:
  - consider emergent nephrectomy after IV ABx started and patient stabilized
- renal obstruction:
  - admit for emergent stenting or percutaneous nephrostomy tube



Nitrofurantoin has poor tissue penetration and therefore is not used to treat pyelonephritis (requires post-renal uroconcentration).

## Prostatitis/Prostatodynia

**Epidemiology**

- most common urologic diagnosis in men <50 yr
- prevalence 2-12%



**4-Glass Test:** Prostatic source is suggested when colony counts in EPS and VB3 exceed those of VB1 and VB2 by 10x.



Prostatic massage may cause extreme tenderness and increased risk of inducing sepsis, abscess, or epididymo-orchitis.



It is not recommended to do a serum PSA during acute bacterial prostatitis.

## Classification

**Table 9. Comparison of the Three Types of Prostatitis**

	Category I: Acute Bacterial Prostatitis	Category II: Chronic Bacterial Prostatitis	Category III: Chronic Pelvic Pain Syndrome (CPPS) (Abacterial)
<b>Etiology</b>	Ascending urethral infection with KEEPS (see U12 sidebar): 80% <i>E. coli</i> Often associated with outlet obstruction, recent cystoscopy, prostatic biopsy Most infections occur in the peripheral zone (see Figure 7)	Recurrent exacerbations of acute prostatitis-like signs and symptoms Recurrent UTI with same organism	Divided into inflammatory (IIIA) and non-inflammatory (IIIB) Intraprostatic reflux of urine $\pm$ urethral hypertonia Multifactorial (immunological, neuropathic, neuroendocrine, psychosocial)
<b>Clinical Features</b>	Acute onset fever, chills, malaise Rectal, lower back and perineal pain LUTS	Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain	Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain
<b>Investigations</b>	PEx: Abdo, external genitalia, perineum, prostate U/A Blood CBC, C&S Transrectal U/S if non-resolving/suspect prostatic abscess	PEx: as per Category I + pelvic floor Urine C&S: 4-glass test VB1 (voided bladder): initial (urethra) VB2: midstream (bladder) EPS (expressed prostatic secretions): not usually performed VB3: post-massage/DRE	Same as per Category II NIH-CPSI score* Consider psychological assessment
<b>Treatment</b>	Supportive measures PO or IV ABx depending how sick (see Table 8) May consider catheterization in pts with severe obstructive LUTS or retention I&D of abscess if present	ABx (see Table 8) Consider addition of an $\alpha$ -blocker	Supportive measures Trial of ABx therapy if newly diagnosed Multi-modal Tx strategy may include: $\alpha$ -blocker Anti-inflammatories Phytotherapy (quercetin, cernilton)

\*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index

## Epididymitis and Orchitis



### Etiology

- common infectious causes:
  - <35 yr: *N. gonorrhoeae* or *Chlamydia trachomatis*
  - $\geq 35$  yr or penetrative anal intercourse: GI organisms (especially *E. coli*)
- other causes:
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)

### Risk Factors

- UTI
- unprotected sexual contact
- instrumentation/catheterization
- reflux
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens  $\rightarrow$  sterile epididymitis
- immunocompromise

### Clinical Features

- sudden onset scrotal pain and swelling  $\pm$  radiation along cord to flank
- scrotal erythema and tenderness
- fever
- storage symptoms, purulent D/C
- reactive hydrocele

### Investigations

- U/A, urine C&S
- $\pm$  urethral D/C: Gram stain/culture
- if diagnosis uncertain, must do:
  - colour-flow Doppler U/S to r/o testicular torsion

### Treatment

- r/o torsion (see *Investigations* and Table 23, U28)
- see Table 8 for ABx therapy
- scrotal support, bed rest, ice, analgesia

### Complications

- if severe  $\rightarrow$  testicular atrophy
- 30% have persistent infertility problems



**Prehn's sign:** pain may be relieved with elevation of testicles in epididymitis but not in testicular torsion. Poor sensitivity, especially in children.



If unsure between diagnoses of epididymitis and torsion, always go to OR.

Remember: torsion > 6 h has poor prognosis



Inadequately treated acute epididymitis may lead to chronic epididymitis or epididymo-orchitis.



## Urethritis

### Etiology

- infectious or inflammatory (e.g. reactive arthritis)

**Table 10. Infectious Urethritis: Gonococcal vs. Non-Gonococcal**

	Gonococcal	Non-gonococcal
<b>Causative organism</b>	<i>Neisseria gonorrhoeae</i>	Usually <i>Chlamydia trachomatis</i>
<b>Diagnosis</b>	Hx of sexual contact, thick, profuse, yellow-grey purulent D/C, LUTS Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen	Hx of sexual contact, mucoid whitish purulent, D/C, $\pm$ storage LUTS Gram stain demonstrates $>4$ PMN/oil immersion field, no evidence of <i>N. gonorrhoeae</i> , urine PCR and/or culture from urethral specimen
<b>Treatment</b>	see Table 8	see Table 8



If culture negative or unresponsive to treatment consider: *Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, HSV, or adenovirus.



**Reactive Arthritis (formerly known as Reiter's syndrome)**  
Urethritis, uveitis and arthritis (can't pee, can't see, can't climb a tree)



## Stone Disease

### Epidemiology

- prevalance of 2-3%
- male:female = 3:1
- peak incidence 30-50 yr of age
- recurrence rate: 10% at one yr, 50% at 5 yr, 60-80% lifetime

### Risk Factors

- hereditary: RTA, G6PD, cystinuria, xanthinuria, oxaluria, etc.
- lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
- medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, and zonisamide
- medical conditions: UTI (with urea-splitting organisms), myeloproliferative disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI  $>30$ )

### Clinical Features

- urinary obstruction  $\rightarrow$  upstream distention  $\rightarrow$  pain
  - flank pain from renal capsular distention (non-colicky)
  - severe waxing and waning pain radiating from flank to groin, testis, or tip of penis due to stretching of collecting system or ureter (ureteral colic)
- writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
- if fever, r/o concurrent pyelonephritis and/or obstruction

**Table 11. Differential Diagnosis of Renal Colic**

GU	Abdominal	Neurological
<ul style="list-style-type: none"> <li>Pyelonephritis</li> <li>Ureteral obstruction from other cause: UPJ obstruction, clot colic secondary to gross hematuria, sloughed papillae</li> <li>Gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, PID</li> </ul>	<ul style="list-style-type: none"> <li>AAA</li> <li>Bowel ischemia</li> <li>Pancreatitis</li> <li>Other acute abdominal crisis</li> </ul>	<ul style="list-style-type: none"> <li>Radiculitis (L1): herpes zoster, nerve root compression</li> </ul>

### Location of Stones

- calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
- pelvis: tend to cause obstruction at UPJ, may cause persistent infection
- ureter:  $<5$  mm diameter will pass spontaneously in 75% of patients

### Stone Pathogenesis

- supersaturation of stone constituents (at appropriate temperature and pH)
- stasis, low flow, and low volume of urine (dehydration)
- crystal formation and stone nidus
- loss of inhibitory factors:
  - citrate (forms soluble complex with calcium)
  - magnesium (forms soluble complex with oxalate)
  - pyrophosphate
  - Tamm-Horsfall glycoprotein



#### Key Points in Stone Hx

- Diet (especially FLUID INTAKE)
- Predisposing medical conditions
- Predisposing medications
- Previous episodes/investigations/treatments
- Family hx (1st degree relative)



The four narrowest passage points for upper tract stones are:

- UPJ
- Pelvic brim
- Under vas deferens/broad ligament
- UVJ



	Radiopaque	Radiolucent
<b>KUB</b>	Calcium Struvite Cystine	Uric acid Indinavir
<b>CT</b>	Calcium Struvite Cystine Uric acid	Indinavir

## Approach to Renal Stone

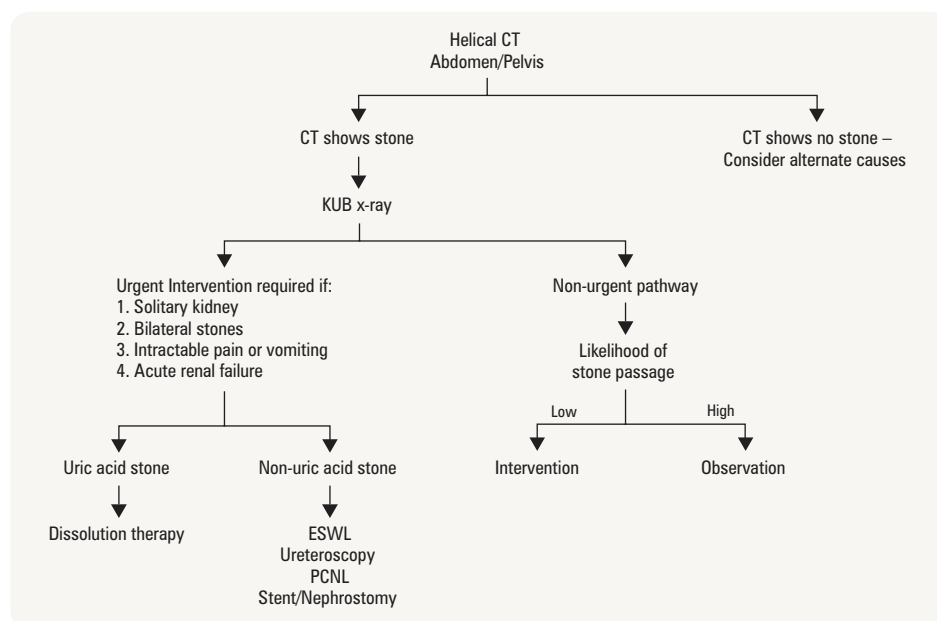


Figure 8. Approach to renal stone

### Investigations

Table 12. Investigations for Renal Stones

	CBC, uric acid, U/A, urine C&S	KUB x-ray	CT scan	Abdominal ultrasound	Cystoscopy	PTH, 24 h urine x 2 for volume, Cr, Ca <sup>2+</sup> , Na <sup>+</sup> , PO <sub>4</sub> <sup>3-</sup> , Mg <sup>2+</sup> , oxalate, citrate, ± cystine
<b>Who gets it?</b>	Everyone	Most	First episode renal colic	Pediatric cases or those concerning for obstruction	± Those concerning for bladder stone	Recurrent Ca <sup>2+</sup> stone formers ± pediatric cases
<b>Why is it done?</b>	May show signs of infection, ± sensitivities	90% of stones are radiopaque Good for follow-up	Distinguish radiolucent stone from soft tissue filling defect X-ray comparison	No radiation Visualize hydronephrosis	Visualize bladder	Need to rule out metabolic cause for stones
<b>Cautions</b>	–	Do not mistake phleboliths for stones!	Radiation Must be a non-contrast scan	Not good at visualizing stones in ureter	–	–

### Treatment – Acute

- medical
  - analgesic ± antiemetic
  - NSAIDs help lower intra-ureteral pressure
  - medical expulsion therapy (MET)
    - ♦ α-blockers: increase rate of spontaneous passage in distal ureteral stones
    - ♦ calcium channel blockers
  - ± Abx for bacteriuria
  - IV fluids if vomiting (note: IV fluids do NOT promote stone passage)
- interventional:
  - required if obstruction endangers patient, e.g. sepsis, renal failure
  - first line: ureteric stent (via cystoscopy)
  - second line: image-guided percutaneous nephrostomy
- admit if necessary:
  - see sidebar: *Indications for Admission to Hospital*

### Treatment – Elective

- medical:
  - likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
    - ♦ stones <5 mm especially likely to pass spontaneously
  - PO fluids to increase urine volume to >2 L/d (3-4 L if cystine) and MET
  - specific to stone type (see Table 13)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)



Detailed metabolic studies are NOT recommended unless complex patient (recurrent stone formers, pregnancy, pediatrics, strong family hx, underlying kidney or systemic disease, etc).



24 h urine collections must be done AFTER discontinuing stone preventing/promoting medications.



#### Indications for Admission to Hospital:

- Intractable pain
- Intractable vomiting
- Fever (suggests infection)
- Compromised renal function (including single kidney, bilateral obstructing stone)
- Pregnancy



#### Stones and Infection

If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared.



#### Efficacy of α-Blockers for the Treatment of Ureteral Stones

*J. Urol* 2007;177:983-987  
**Study:** Meta-analysis of prospective randomized trials comparing α-blockers to conservative therapy.  
**Methods:** MEDLINE, the Cochrane Central Search library, EMBASE, and the electronic database of abstracts presented at the Annual Meeting of the American Urological Association were searched for literature published in English. 11 studies met selection criteria (n=911). Treatment ranged from 8 d-6 wk. Outcome of interest was incidence of distal ureteral stone expulsion.  
**Results:** Administration of an α-blocker with conservative treatment increased incidence of stone expulsion over conservative treatment alone by 44% (95% CI 1.31-1.59, p<0.001).  
**Conclusion:** α-blocker therapy is associated with significantly increased rates of distal ureteral stone expulsion.



Although hypercalciuria is a risk factor for stone formation, decreasing dietary calcium is NOT recommended to prevent stone formation. Low dietary calcium leads to increased GI oxalate absorption and higher urine levels of calcium oxalate.

- interventional:
  - kidney
    - ♦ may stent prior to ESWL if stone is 1.5-2.5 cm
    - ♦ ESWL if stone <2 cm
    - ♦ PCNL if stone >2 cm (see sidebar)
  - ureteral stones >10 mm
    - ♦ ESWL and URS are both first line treatment modalities for all locations
      - URS has significantly greater stone-free rates for stones at all locations in ureter, but also has higher complication rates (ureter perforation, stricture formation, etc.)
    - ♦ PCNL is second line treatment
    - ♦ laparoscopic or open stone removal (very rare)
  - bladder
    - ♦ transurethral stone removal or cystolitholapaxy
    - ♦ remove outflow obstruction (TURP or stricture dilatation)

**Indications for PCNL**

- Size > 2 cm
- Staghorn
- UPJ obstruction
- Calyceal diverticulum
- Cystine stones (poorly fragmented with ESWL)
- Anatomical abnormalities
- Failure of less invasive modalities

**Prevention**

- dietary modification:
  - increase fluid (>2 L/d), K<sup>+</sup> intake
  - reduce animal protein, oxalate, Na<sup>+</sup>, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
- medications:
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria



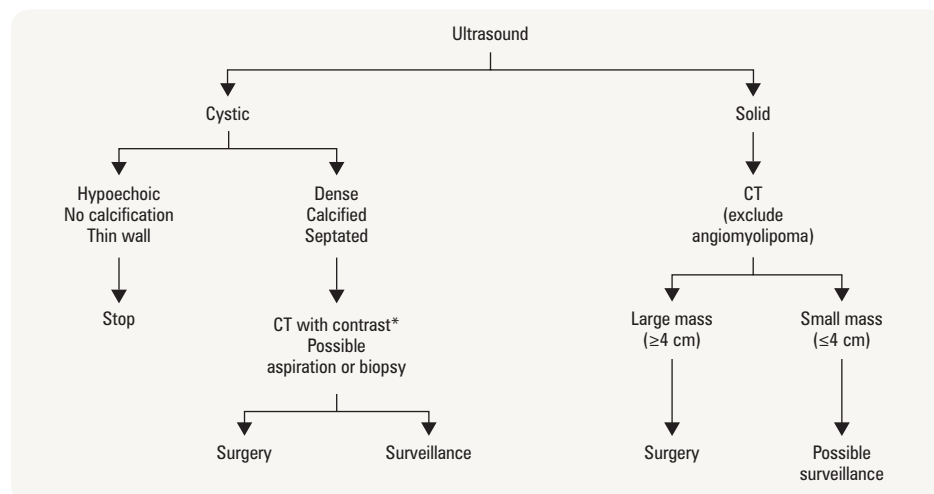
Consideration must be given to monitoring stone formers with periodic imaging (i.e. at year 1 and then q2-4yr based on likelihood of recurrence).

**Table 13. Stone Classification**

Type of Stone	Calcium (75-85%)	Uric Acid (5-10%)	Struvite (5-10%)	Cystine (1%)
<b>Etiology</b>	Hypercalciuria Hyperuricosuria (25% of patients with Ca <sup>2+</sup> stones) Hyperoxaluria (<5% of patients) Hypocitraturia (12% of patients) Other causes: • Hypomagnesemia – associated with hyperoxaluria and hypocitraturia • High dietary Na <sup>+</sup> • Decreased urinary proteins • High urinary pH, low urine volume (e.g. GI water loss) • Hyperparathyroidism, obesity, gout, DM	Uric acid precipitates in low volume, acidic urine with a high uric acid concentration: • Hyperuricosuria alone • Low urinary pH, low urine volume (e.g. GI water loss) • Drugs (ASA, thiazides) • Diet (purine rich red meats) • Hyperuricosuria with hyperuricemia • Gout • High rate of cell turnover or cell death (leukemia, cytotoxic drugs)	Infection with urea-splitting organisms ( <i>Proteus</i> , <i>Pseudomonas</i> , <i>Providencia</i> , <i>Klebsiella</i> , <i>Mycoplasma</i> , <i>Serratia</i> , <i>S. aureus</i> ) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)	Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in “COLA” in urine (cystine, ornithine, lysine, arginine)
<b>Key Features</b>	Radiopaque on KUB Reducing dietary Ca <sup>2+</sup> is NOT an effective method of prevention/treatment	Radiolucent on KUB Radiopaque on CT Acidic urine, pH < 5.5 (NOT necessarily elevated urinary uric acid)	Perpetuates UTI because stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: <i>E. coli</i> infection does not cause struvite stones 3:1 (M:F), UTI more common in female	Aggressive stone disease seen in children and young adults Recurrent stone formation, family hx Often staghorn calculi Faintly radiopaque on KUB Positive urine sodium nitroprusside test, urine chromatography for cystine
<b>Treatment</b> Medical if stone <5 mm and no complications  Procedural/Surgical treatment if stone >5 mm or presence of complications (see U17 for treatment)	Fluids to increase urine volume to >2 L/d For calcium stones: cellulose phosphate, orthophosphate for absorptive causes Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol Calcium struvite: ABx (stone must be removed to treat infection)	Increased fluid intake Alkalinization of urine to pH 6.5 to 7 (bicarbonate, potassium citrate) ± allopurinol	Complete stone clearance ABx for 6 wk Regular F/U urine cultures	Increased fluid intake (3-4 L of urine/d) Alkalinize urine (bicarbonate, potassium citrate), Penicillamine/α-MPG or Captopril (form complex with cystine) ESWL not effective

# Urological Neoplasms

## Approach to Renal Mass



**Figure 9. Workup of a renal mass**

\*Imaging modality may be different in cases of contrast allergy or elevated creatinine



There is controversy over optimal management of small renal masses.

## Benign Renal Neoplasms

### CYSTIC KIDNEY DISEASE

- **simple cysts:** usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - **Bosniak Classification** is used to stratify for risk of malignancy based on cyst features from contrast CT (see Table 14)
- **polycystic kidney disease**
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure
- **medullary sponge kidney:** cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- **von Hippel-Lindau syndrome:** multiple bilateral cysts or clear cell carcinomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas



#### Tuberous Sclerosis

Syndrome characterized by mental retardation, epilepsy, and adenoma sebaceum. 45-80% of patients also present with angiomyolipomas which are often multiple and bilateral.



Percutaneous needle biopsies of cystic renal masses may lead to peritoneal seeding.

**Table 14. Bosniak Classification of Renal Cysts**

Class	Description	Features	Risk of Malignancy	Management Plan
I	Simple cyst	Round, no septations, no calcifications, no solid component	Near zero	F/U usually not required
II	Simple cyst	A few thin septa, no true enhancement, well-marginated, uniform high attenuation, <3 cm	Minimal	F/U usually not required
IIIF	Minimally complex cyst with extra features that require F/U	Still well-marginated and non-enhancing, but now multiple thin septa or some thickening/calcification of septa/wall, >3 cm	5-20%	Requires F/U with imaging q6-12 mo If the lesion evolves, may require surgical resection
III	Complex cyst	Thicker or more irregular walls with measurable enhancement	>50%	Requires surgical resection
IV	Clearly malignant	Class III + enhancing soft-tissue components	>90%	Requires surgical resection

Table 15. Benign Renal Masses

	Angiomyolipoma (Renal Hamartoma)	Renal Oncocytoma	Renal Adenoma
<b>Epidemiology</b>	<1% of adult renal tumours F>M 20% associated with tuberous sclerosis (especially if multiple, recurrent)	3-7% of renal tumours M>F Oncocytomas also found in adrenal, thyroid and parathyroid glands	Most common benign renal neoplasm M:F = 3:1 Incidence increases with age Found in 7-23% of all autopsies
<b>Characteristics</b>	Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma) May extend into regional lymphatics and other organs and become symptomatic	Spherical, capsulated with possible central scar Histologically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct	Small cortical lesions <1 cm Majority are solitary but can be multifocal
<b>Diagnosis</b>	Incidental finding on CT Negative attenuation (-20 HU) on CT is pathognomonic Rare presentation of hematuria, flank pain, and palpable mass (same as RCC)	Incidental finding on CT Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise Biopsy may be performed to r/o malignancy	Incidental finding on CT Rarely symptomatic Controversy as to whether this represents benign or pre-malignant neoplasm
<b>Management</b>	May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy) Follow with serial U/S	Partial/radical nephrectomy for large masses HIFU or RFA for smaller masses	If mass >3 cm, likely not a benign adenoma; will require partial/radical nephrectomy due to increased likelihood of malignancy

## Malignant Renal Neoplasms



### RENAL CELL CARCINOMA (RCC)

#### Etiology

- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

#### Epidemiology

- 8th most common malignancy (accounts for 3% of all newly diagnosed cancers)
- 85% of primary malignant tumours in kidney
- male:female = 3:2
- peak incidence at 50-60 yr of age

#### Pathology

- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobic (5-10%), collecting duct
- sarcomatoid elements in any subtype is a poor prognostic factor

#### Risk Factors

- top 3 risk factors: smoking, HTN, obesity
- miscellaneous: horseshoe kidney, acquired renal cystic disease

#### Clinical Features

- usually asymptomatic: frequently diagnosed incidentally by U/S or CT
- poor prognostic indicators: weight loss, weakness, anemia, bone pain
- classic “too late triad” found in 10-15%:
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- was called the “internist’s tumour” because of paraneoplastic symptomatology (see sidebar) – now called the “radiologist’s tumour” because of incidental diagnosis via imaging
- metastases: seen in 1/3rd of new cases; additional 20-40% will go on to develop metastases
  - bone, brain, lung and liver most common sites

#### Investigations

- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A (60-75% have hematuria)
- renal U/S: solid vs. cystic lesion
- CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
- MRI: useful for evaluation of vascular extension
- FNA: to confirm diagnosis if considering observation or other non-surgical therapy

#### Staging

- involves CT, CXR, liver enzymes and LFTs, bone scan

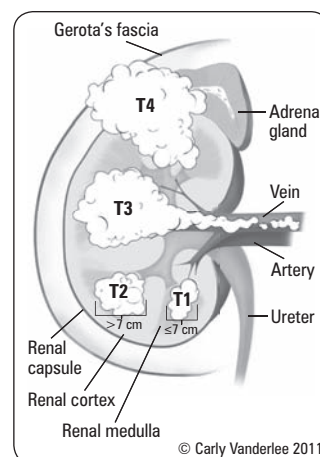


Figure 10. RCC staging



Role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC.



**RCC Systemic Effects:** paraneoplastic syndromes (10-40% of patients)

- Hematopoietic disturbances: anemia, polycythemia, raised ESR
- Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)
- Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour
- Hemodynamic alterations: systolic HTN (due to AV shunting), peripheral edema (due to caval obstruction)

**Table 16. 2010 TNM Classification of Renal Cell Carcinoma**

T	N	M
<b>T1:</b> tumour <7 cm, confined to renal parenchyma <b>T1a:</b> <4 cm <b>T1b:</b> 4-7 cm <b>T2:</b> tumour >7 cm, confined to renal parenchyma <b>T2a:</b> tumour >7 cm but ≤10 cm in greatest dimension, limited to the kidney <b>T2b:</b> tumour >10 cm, limited to the kidney <b>T3:</b> tumour extends into major veins or perinephric tissues, but NOT into ipsilateral adrenal or beyond Gerota's fascia <b>T3a:</b> into renal vein or sinus fat <b>T3b:</b> into infradiaphragmatic IVC <b>T3c:</b> into supradiaphragmatic IVC <b>T4:</b> tumour extends beyond Gerota's fascia including extension into ipsilateral adrenal	<b>N0:</b> no regional nodes <b>N1:</b> metastasis to a single node, <2 cm <b>N2:</b> metastasis to a single node between 2 and 5 cm or multiple nodes <2 cm <b>N3:</b> node >5 cm	<b>M0:</b> no evidence of metastasis <b>M1:</b> presence of distant metastasis

**Treatment**

- surgical
  - radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota's capsule and paraaortic lymphadenectomy
  - partial nephrectomy (parenchyma-sparing): <4 cm tumour or solitary kidney/bilateral tumours
  - surgical removal of solitary metastasis may be considered
- ablative techniques (cryoablation, RFA)
- palliative radiation to painful bony lesions
- therapy for advanced stage:
  - anti-angiogenesis/anti-VEGF (e.g. bevacizumab)
  - mTOR inhibitors (e.g. temsirolimus, everolimus)
  - high-dose IL-2 (high toxicity but able to induce long-term remission in 10% of patients)
  - IFN α: monotherapy has been largely replaced by molecularly targeted agents listed above
  - tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)

**Prognosis**

- stage at diagnosis most important prognostic factor:
  - T1: 90-100% 5-yr survival
  - T2-T3: 60% 5-yr survival
  - metastatic disease: <5% 10-yr survival



Tumour may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli.



**Sorafenib in Advanced Clear-Cell Renal Cell Carcinoma – TARGET Trial**  
*NEJM* 2007;356:125-134

**Study:** Phase III, double-blind RCT comparing multikinase inhibitor, sorafenib, with placebo in treatment of advanced clear-cell renal cell carcinoma.

**Methods:** Patients with clear cell renal cell carcinoma, resistant to standard therapy. The main intervention and outcome were sorafenib and overall survival, respectively.

**Results:** Progression-free survival in intervention group was 5.5 mo, compared with 2.8 mo in the placebo group. The survival improvement was associated with an increased number of adverse events.



**Differential Diagnosis of Filling Defect**

- Urothelial cell carcinoma (differentiate via cytology and CT scan)
- Uric acid stone (differentiate via cytology and CT scan)
- Blood clot
- Pyelitis cystica
- Papillary necrosis
- Fungus ball
- Gas bubble from gas producing organisms

## Carcinoma of the Renal Pelvis and Ureter

**Etiology**

- risk factors include:
  - smoking
  - chemicals/dietary exposures (industrial dyes and solvents; aristolochic acid)
  - analgesic abuse (acetaminophen, ASA, and phenacetin)
  - Balkan nephropathy

**Epidemiology**

- rare: accounts for 5% of all urothelial cancers
- frequently multifocal, 2-5% are bilateral
- M:F = 3:1
- relative incidence: bladder:renal:ureter = 100:10:1

**Pathology**

- 85% are papillary urothelial carcinoma (TCC); others include SCC and adenocarcinoma
- TCC of ureter and renal pelvis are histologically similar to bladder TCC

**Clinical Features**

- gross/microscopic hematuria
- flank pain
- storage or voiding symptoms (dysuria only if lower urinary tract involved)
- flank mass ± hydronephrosis (10-20%)

**Investigations**

- IVP/CT urogram
- cystoscopy and retrograde pyelogram

**Treatment**

- radical nephroureterectomy with cuff of bladder
- distal ureterectomy for distal ureteral tumours



## Bladder Carcinoma



### Etiology

- unknown, but environmental risk factors include:
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior hx of radiation treatment to the pelvis
  - Schistosoma hematobium* infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)



The “field defect” theory helps to explain why TCC has multiple lesions and has a high recurrence rate. The entire urothelium (pelvis to bladder) is bathed in carcinogens.

### Epidemiology

- 2nd most common urological malignancy
- male:female = 3:1, white:black = 4:1
- mean age at diagnosis is 65 yr

### Pathology

- classification:
  - TCC >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis:
  - non-muscle invasive (75%) → >80% overall survival
    - 15% of these will progress to invasive TCC
    - the majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5-yr survival
    - 85% have no prior hx of superficial TCC (i.e. *de novo*)
    - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma *in situ* → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive TCC

### Clinical Features

- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumour (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider carcinoma in situ
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting, and diarrhea)



The ENTIRE urinary tract must be evaluated in patients with hematuria unless there is clear evidence of glomerular bleeding (e.g. red cell casts, dysmorphic RBCs, etc.).

### Investigations

- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast or IVP → look for filling defect
- cystoscopy with bladder washings (gold standard)
- biopsy to establish diagnosis and to determine depth of penetration
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP)



Unexplained hematuria in any individual >40 yr old must be investigated to r/o a malignancy.

### Grading

- Grade 1: well-differentiated (10% invasive)
- Grade 2: moderately differentiated (50% invasive)
- Grade 3: poorly differentiated (80% invasive)



Cystoscopy is the initial procedure of choice for the diagnosis and staging of urothelial malignancy.

### Staging

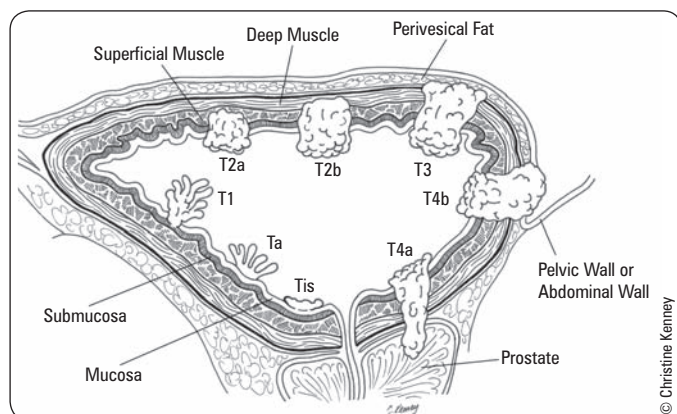
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes (metastatic work-up)



Tumour grade is the single most important prognostic factor for progression.

**Table 17. 2010 TNM Classification of Bladder Carcinoma (see Figure 11)**

T	N	M
<b>Ta:</b> noninvasive papillary carcinoma <b>Tis:</b> carcinoma in situ (CIS); flat tumour <b>T1:</b> tumour invades submucosa/lamina propria <b>T2a:</b> tumour invades superficial muscle <b>T2b:</b> tumour invades deep muscle <b>T3a:</b> tumour invades perivesical tissue (microscopic) <b>T3b:</b> tumour invades perivesical tissue (macroscopic) <b>T4a:</b> adjacent organ involvement; prostate, uterus, or vagina <b>T4b:</b> adjacent organ involvement; pelvic wall or abdominal wall	<b>N status:</b> as for RCC	<b>M status:</b> as for RCC

**Figure 11. Urothelial carcinoma of bladder****Treatment**

- superficial (non-muscle invasive) disease: Tis, Ta, T1
  - TURBT ± single dose or 6-wk course of intravesical chemo/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
  - maintenance with intravesical chemotherapy with BCG may be continued for 2-3 yr
  - high grade disease: TURBT + maintenance BCG OR cystectomy in select patients
- invasive disease: T2a, T2b, T3
  - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileal conduit, Indiana pouch, ileal neobladder) or TURBT + chemo-radiation for small tumours
  - neo-adjuvant chemotherapy prior to cystectomy may also be done
  - use of adjuvant chemotherapy after definitive local treatment is controversial
- advanced/metastatic disease: T4a, T4b, N+, M+
  - initial combination of systemic chemotherapy ± irradiation ± surgery

**Prognosis**

- depends on stage, grade, size, number of lesions, recurrence and presence of CIS:
  - T1: 90% 5-yr survival
  - T2: 55% 5-yr survival
  - T3: 20% 5-yr survival
  - T4/N+/M+: <5% 5-yr survival

**Prostatic Carcinoma (CaP)****Etiology**

- not known
- risk factors
  - increased incidence in persons of African descent
  - high dietary fat = 2x risk
  - family hx
    - ♦ 1st degree relative = 2x risk
    - ♦ 1st and 2nd degree relatives = 9x risk

**Epidemiology**

- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between ages of 60 and 85; mean age at diagnosis is 72

**Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer**

NEJM 2003;349:859-866

Study: Randomized clinical trial.

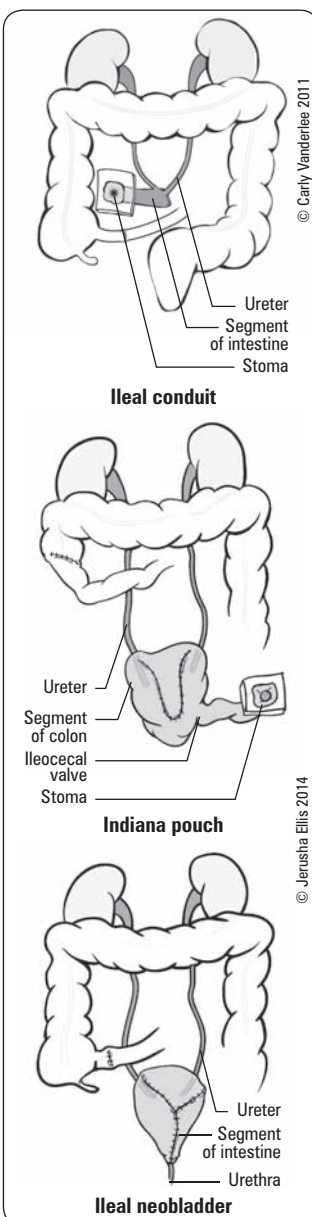
Patients: 317 patients with transitional-cell carcinoma of the bladder (T2N0M0 to T4aN0M0).

Intervention: Randomized to undergo radical cystectomy or to receive three cycles of combined chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin) followed by radical cystectomy.

Main outcome: Survival. Secondary objective was to quantify down-staging of tumour following chemotherapy.

Results: At 5 yr after treatment initiation, 57% of the combination-therapy group vs 43% of the cystectomy group were alive ( $p=0.06$ ). In the combination-therapy group, 38% of the patients were pathologically free of cancer at the time of cystectomy vs. 15% of the cystectomy-only group at the time of surgery ( $p<0.001$ ).

Conclusions: For locally advanced bladder carcinoma, neoadjuvant chemotherapy significantly reduces tumour volume and also improves survival.

**Figure 12. Ileal conduit, Indiana pouch, ileal neobladder**

## Pathology

- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma (4.5%)
  - associated with TCC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle

## Anatomy (see Figure 7)

- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

## Clinical Features

- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see *CaP Screening*, U25
- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
- metastatic disease:
  - bony mets to axial skeleton common
  - visceral mets are less common (liver, lung, and adrenal gland most common sites)
  - leg pain and edema with nodal mets obstructing lymphatic and venous drainage

## Methods of Spread

- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

## Investigations

- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan may be omitted in untreated CaP with PSA <10 ng/mL
- CT scanning to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsying and active surveillance

**Table 18. 2010 TNM Classification of Prostate Carcinoma**

T	N	M
<b>T1:</b> clinically undetectable tumour, normal DRE and TRUS <b>T1a:</b> tumour incidental histologic finding in <5% of tissue resected <b>T1b:</b> tumour incidental histologic finding in >5% of tissue resected <b>T1c:</b> tumour identified by needle biopsy (because of elevated PSA level) <b>T2:</b> palpable, confined to prostate <b>T2a:</b> tumour involving ≤ one half of one lobe <b>T2b:</b> tumour involving > one half of one lobe, but not both lobes <b>T2c:</b> tumour involving both lobes <b>T3:</b> tumour extends through prostate capsule <b>T3a:</b> extracapsular extension (unilateral or bilateral) <b>T3b:</b> tumour invading seminal vesicle(s) <b>T4:</b> tumour invades adjacent structures (besides seminal vesicles)	<b>NX:</b> regional lymph nodes were not assessed <b>N0:</b> no regional lymph node metastasis <b>N1:</b> spread to regional lymph nodes	<b>M0:</b> no distant metastasis <b>M:</b> distant metastasis <b>M1a:</b> nonregional lymph nodes <b>M1b:</b> bone(s) <b>M1c:</b> other site(s) with or without bone disease

**Table 19. Prostate Cancer Mortality Risk**

	Low Risk	Moderate Risk (if any of following)	High Risk (if any of following)
PSA	<10	10-20	>20
Gleason Score	<7	7	8-10
Stage	pT1-2a	pT2b-T2c	pT3/4

## Treatment

- T1/T2 (localized, low-risk)
  - if adequate life expectancy or no other significant co-morbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - no difference in cure rate between definitive treatment modalities
  - in older population: watchful waiting + palliative treatment for symptomatic progression
- T1/T2 (intermediate or high-risk)
  - definitive therapy over active surveillance
- T3, T4
  - EBRT + androgen deprivation therapy or RP + adjuvant EBRT
- N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bilateral orchiectomy – removes 90% of testosterone
  - GnRH agonists (e.g. leuprolide, goserelin)
  - estrogens [e.g. diethylstilbestrol (DES)]
  - antiandrogens (bicalutamide)
  - local irradiation of painful secondaries or half-body irradiation
- hormone-refractory prostate cancer
  - chemotherapy: docetaxel, cabazitaxel, sipuleucel-T

**Table 20. Treatment Options for Localized Prostate Cancer**

Modality	Population Considered	Limitations
Watchful Waiting	Short life expectancy (<5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses	Disease progression
Active Surveillance (serial PSA, DRE, and biopsies)	Low grade disease, good F/U; is still considering more curative treatment if disease progresses	Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date
Brachytherapy	Low volume, low PSA (<10), low grade	ED (50%), long term effectiveness not well-established
EBRT	Locally advanced disease, older patients	Radiation proctitis (5%), ED (50%), risk of rectal cancer
RP	Young patients (<75 yr), high-risk disease	Incontinence (10%), ED (30-50%)

\*Other options include cryosurgery, HIFU, hormonal ablation

## Prognosis

- T1-T2: comparable to normal life expectancy
- T3-T4: 40-70% 10-yr survival
- N+ and/or M+: 40% 5-yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

## CaP Screening

### Digital Rectal Exam (DRE)

- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

### Prostate Specific Antigen (PSA)

- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in setting of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cutpoint
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- PSA velocity, PSA density, and free:total PSA: all intended to increase sensitivity and specificity of serum PSA values

### Screening Recommendations

- conflicting evidence regarding mortality reduction with PSA-based screening and debate regarding overdiagnosis/overtreatment
- Ontario Ministry of Health and Long-Term Care and United States Preventative Services Task Force both recommend against PSA testing as a population-wide screening tool
- serum PSA determination recommended in any man with >10 yr life-expectancy and any of the following:
  - suspicious finding on DRE (see above)
  - moderate-severe LUTS
  - investigating secondary carcinoma of unknown origin to r/o CaP as primary



#### Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer (Scandinavian Prostate Cancer Group Study)

NEJM 2011;364:1708-1717

**Study:** Randomized clinical trial comparing watchful waiting with radical prostatectomy for localized prostate cancer.

**Methods:** 695 men from 14 centres in Finland, Sweden, and Iceland with newly diagnosed, localized prostate cancer were included in this study.

**Main outcomes:** Mortality, distant metastases, local progression.

**Results:** For men with low-risk prostate cancer (PSA <10, Gleason score <7), at 15 yr after treatment initiation, the relative risk of death due to prostate cancer in the radical prostatectomy group versus watchful waiting was 0.62 (p=0.01). The cumulative incidence of death from prostate cancer after radical prostatectomy was high as compared with other studies.

**Conclusions:** Radical prostatectomy was associated with reduced rate of death due to prostate cancer.



#### Radical Prostatectomy versus Observation for Localized Prostate Cancer. (Prostate Cancer Intervention versus Observation Trial (PIVOT) Study Group)

NEJM 2012;367:203-213

**Study:** Randomized clinical trial comparing observation with radical prostatectomy for localized prostate cancer.

**Methods:** 731 men at 52 United States centres with localized prostate cancer participated.

**Main outcomes:** Mortality, bone metastases, surgical morbidity.

**Results:** Radical prostatectomy did not reduce all-cause or prostate cancer mortality relative to observation (relative risk 0.60, p=0.09), through at least 12 yr of follow-up.

**Conclusions:** Observation is recommended for localized prostate cancer, especially in men with low PSA and low-risk disease.



PSA is specific to the PROSTATE, but NOT to prostate cancer.



#### Causes of Increased PSA

BPH, prostatitis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy.

**Canadian Urological Association Guidelines (2011) re: CaP Screening**

- harms and benefits of PSA testing must be explained to the patient and an informed, shared decision to test must be established
- initial screening should include both serum PSA and DRE
- all men should be offered screening at age 50 if >10 yr life-expectancy
- high-risk individuals (family hx of CaP or African ancestry) should be offered screening at age 40 if >10 yr life-expectancy
- standard has been annual screening, but q2-4 yr screening acceptable
- no strict cutpoint for when to biopsy. Decision to biopsy should be based on more than a single PSA value
- \*new guidelines under development, however, AUA guidelines recommend against universal routine PSA screening for CaP

**Screening for Prostate Cancer.**

*Cochrane DB Syst Rev* 2013;1:CD004720

**Background:** Screening for prostate cancer has an unclear benefit for reducing prostate cancer-specific mortality and morbidity.

**Study:** Systematic review of randomized clinical trials of screening vs no screening. A total of 31 trials were retrieved for this review.

**Results:** A meta-analysis of 5 RCTs with 341,342 participants was done. Collectively, there was no significant reduction in prostate cancer-specific mortality within 10 yr of follow-up. Screening procedures and biopsies were commonly associated with bleeding, bruising, and short-term anxiety; subsequent over-diagnosis and overtreatment resulted in additional harms, some severe.

**Conclusions:** Men who have a life expectancy less than 10 to 15 yr should be informed that screening for prostate cancer is unlikely to be beneficial. Significant harms are associated with screening, over-diagnosis, and overtreatment.

## Testicular Tumours

**Etiology (Risk Factors)**

- cryptorchidism, atrophy, sex hormones, HIV infection, infertility, family hx, past hx of testicular cancer

**Epidemiology**

- rare, but most common solid malignancy in young males 15-34 yr
- any solid testicular mass or acute hydrocoele in young patient – must r/o malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously or successively)

**Pathology**

- primary:
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumours (all are malignant)
    - ♦ seminoma (35%) → classic, anaplastic, spermatocytic
    - ♦ NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<<1%), mixed cell type (40%)
  - 5% are non-germ cell tumours (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary:
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

**Clinical Features**

- **painless** testicular enlargement (painful if intratesticular hemorrhage or infarction)
- dull, heavy ache in lower abdomen, anal area or scrotum
- associated hydrocele (10%)
- coincidental trauma (10%)
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumour effects
- supraclavicular and inguinal lymphadenopathy
- abdominal mass (retroperitoneal lymph node mets)

**Methods of Spread**

- local spread follows lymphatics:
  - right → medial, paracaval, anterior and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - “cross-over” metastases from right to left are fairly common, but no reports from left to right
- hematogenous most commonly to lung, liver, bones, and kidney

**Investigations**

- diagnosis is established by radical inguinal orchidectomy
- tumour markers:
  - $\beta$ -hCG and AFP are positive in 85% of non-seminomatous tumours
  - elevated marker levels return to normal post-operatively if no secondaries
  - $\beta$ -hCG positive in 7% of seminomas, AFP never elevated with seminoma
- testicular U/S (hypoechoic area within tunica albuginea = high suspicion of testicular cancer)
- evidence of testicular microlithiasis is not a risk factor for testicular cancer
- needle aspiration contraindicated

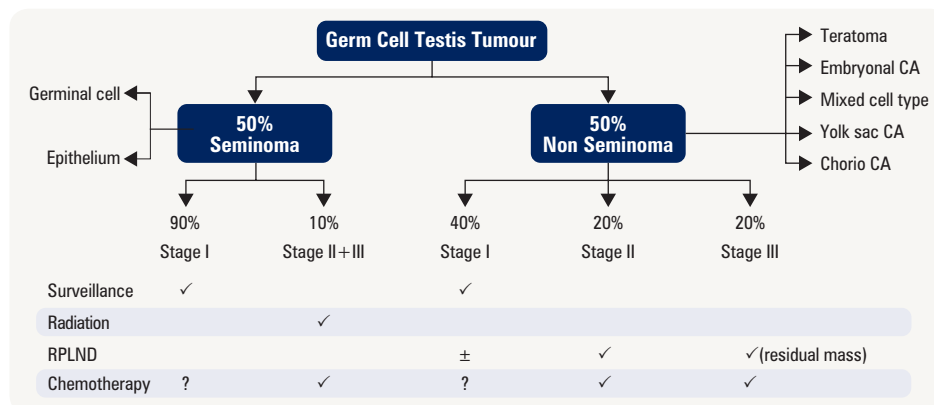
**Management**

- orchiectomy through inguinal ligament for all stages
- consider sperm banking
- adjuvant therapies (see Figure 13)



**Table 21. 2010 TNM Classification of Testicular Carcinoma**

T	N	M
<b>Tis:</b> intratubular germ cell neoplasia <b>T1:</b> limited to testis and epididymis w/o vascular /lymphatic invasion <b>T2:</b> limited to testis and epididymis w/ vascular/lymphatic invasion <b>T3:</b> invasion of the spermatic cord ± vascular/lymphatics <b>T4:</b> invasion of the scrotum ± vascular/lymphatics	N status: same as RCC	<b>M0:</b> no distant mets <b>M1:</b> distant mets <b>M1a:</b> nonregional lymph node(s) or pulmonary mets <b>M1b:</b> distant mets other than to regional lymph nodes and lung

**Figure 13. Adjuvant management of testicular cancer post-orchietomy**

Adapted from Dr. MAS Jewett

**Prognosis**

- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

**Penile Tumours****Epidemiology**

- rare (<1% of cancer in males in U.S.)
- most common in 6th decade

**Benign**

- cyst, hemangioma, nevus, papilloma

**Pre-malignant**

- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumour (large condyloma)

**Pre-invasive Cancer**

- carcinoma *in situ* (CIS):
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil

**Malignant**

- risk factors:
  - chronic inflammatory disease
  - STI
  - phimosis
  - uncircumcised penis
- 2% of all urogenital cancers
- SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion
- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous

**Treatment**

- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
- consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available

**Orchiopexy**

Surgical descent (orchiopexy) of undescended testis does not reduce the risk of malignancy. It can reduce the risk of infertility and allows for early detection of tumours by self-exam.



Testes and scrotum have different lymphatic drainage, therefore trans-scrotal approach for biopsy or orchiectomy should be avoided.

**Staging**

Clinical: CXR (lung mets), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)

- Stage I: disease limited to testis, epididymis, or spermatic cord
- Stage II: disease limited to the retroperitoneal nodes
- Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

Pathologic (at orchiectomy)

- T1: confined to testis and epididymis, no vascular/lymphatic invasion
- T2: extends beyond tunica albuginea or vascular/lymphatic invasion
- T3: involves spermatic cord
- T4: invades scrotum
- T4a: invades spermatic cord
- T4b: invades scrotal wall



## Scrotal Mass

Table 22. Differentiating between Scrotal Masses

Condition	Pain	Palpation	Additional Findings
<b>Torsion</b>	+	Diffuse tenderness Horizontal lie of testicle	Absent cremaster reflex, negative Prehn's sign
<b>Epididymitis (U15)</b>	+	Epididymal tenderness	Present cremaster reflex, positive Prehn's sign
<b>Orchitis (U15)</b>	+	Diffuse tenderness	Present cremaster reflex, positive Prehn's sign
<b>Hematocele</b>	+	Diffuse tenderness	No transillumination
<b>Hydrocele</b>	–	Testis not separable from hydrocele, cord palpable	Transillumination, hx of trauma
<b>Spermatocele</b>	–	Testis separable from spermatocele, cord palpable	Transillumination
<b>Varicocele</b>	–	Bag of worms	No transillumination, increases in size with Valsalva, decrease in size if supine
<b>Indirect Inguinal</b>	– (+ if strangulated)	Testis separable from hernia, cord not palpable, cough impulse may transmit, may be reducible	No transillumination
<b>Tumour</b>	– (+ if hemorrhagic)	Hard lump/nodule	
<b>Generalized/Dependant edema</b>	–	Diffuse swelling	Often post-op or immobilized, check for liver dysfunction
<b>Idiopathic</b>	–		



### Differential of a Benign Scrotal Mass

#### HIS BITS

**Hydrocele**  
Infection (epididymitis/orchitis)  
**Sperm** (spermatocele)  
**Blood** (hematocele)  
Intestines (hernia)  
**Torsion**  
Some veins (varicocele)



Acute scrotal swelling/pain in young boys is torsion until proven otherwise.



Transillumination refers to if light is able to transmit through tissue (i.e. due to excess fluid).



#### Varicocele Grading

- Grade 1: Palpable only with Valsalva manoeuvre
- Grade 2: Palpable without Valsalva
- Grade 3: Visible through scrotal skin

Table 23. Benign Scrotal Masses

Type	Varicocele	Spermatocele	Hydrocele	Testicular Torsion	Inguinal Hernia
<b>Definition</b>	Dilatation and tortuosity of pampiniform plexus	A benign, sperm filled epididymal retention cyst	Collection of serous fluid that results from a defect or irritation in the tunica vaginalis	Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction	Protrusion of abdominal contents through the inguinal canal into the scrotum
<b>Etiology</b>	15% of men Due to incompetent valves in the testicular veins 90% left sided	Multiple theories, including: Distal obstruction Aneurysmal dilations of the epididymis Agglutinated germ cells	Usually idiopathic Found in 5-10% testicular tumours Associated with trauma/infection Communicating: patent processus vaginalis, changes size during day (peds) Non-communicating: non-patent processus vaginalis (adult)	Trauma Cryptorchidism "Bell clapper deformity" Many occur in sleep (50%) Necrosis of glands in 5-6 h	Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness
<b>Hx/P/E</b>	"Bag of worms" Often painless Pulsates with Valsalva	Non-tender, cystic mass Transilluminates	Non-tender, intrascrotal mass Cystic Transilluminates	Acute onset severe scrotal pain, swelling GI upsets cases Retracted and transverse testicle (horizontal lie) Negative Phren's sign Absent cremasteric reflex	A small bulge in the groin that may increase in size and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising
<b>Investigations</b>	P/E Valsava	P/E U/S to r/o tumour	U/S to r/o tumour	U/S with colour flow Doppler probe over testicular artery Decrease uptake on <sup>99m</sup> Tc-pertechnetate scintillation scan (doughnut sign)	Hx and P/E Invagination of the scrotum Valsalva
<b>Treatment</b>	Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (balloon, sclerosing agents) Repair may improve sperm count/motility 50-75%	Conservative Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum Excise if symptomatic	Conservative Needle drainage Surgical	Emergency manual detorsion (rotate outward) with elective bilateral orchiopexy Failure of manual detorsion: surgical detorsion with orchiopexy Orchiectomy if poor prognosis	Surgical repair

**TORSION OF TESTICULAR APPENDIX**

- twisting of testicular/epididymal vestigial appendix

**Signs and Symptoms**

- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
- “blue dot sign”:
  - blue infarcted appendage seen through scrotal skin (can usually be palpated as small, tender lump)

**Treatment**

- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

**HEMATOCELE**

- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

**Treatment**

- ice packs, analgesics, surgical repair



**Suspect a Retroperitoneal Mass/Process in a Patient with a Varicocele if:**

- Acute onset
- Right sided (isolated)
- Palpable abdominal mass
- Doesn't reduce while supine



**Indications for Treatment of Varicocele**

- Impaired sperm quality or quantity
- Pain or dull ache affecting QOL
- Affected testis fails to grow in adolescents
- Cosmetic indications (especially in adolescents)

## Penile Complaints

### Peyronie's Disease

**Definition**

- benign curvature of penile shaft secondary to fibrous thickening of tunica albuginea
- most commonly on dorsal surface resulting in upward curvature of erect penis

**Etiology**

- exact etiology unknown
- trauma/repeated microtrauma → inflammation → fibrosis
- familial predisposition
- associated with DM, vascular disease, autoimmunity, Dupuytren's contracture, erectile dysfunction
- unclear role of vitamin E deficiency,  $\beta$ -blockade, elevated serotonin

**Clinical Features**

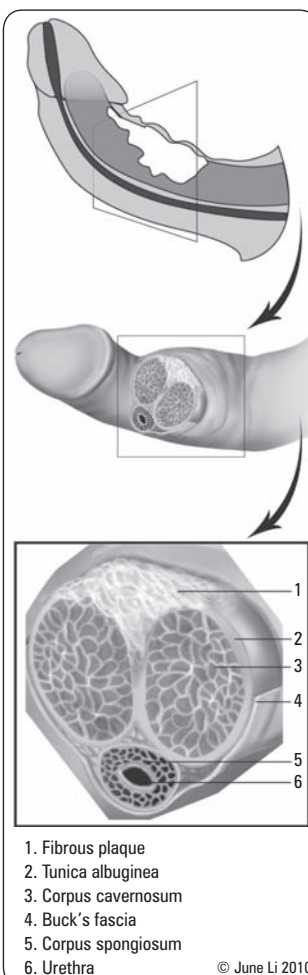
- penile curvature and/or pain with erection
- penile shortening and poor erection distal to plaque

**Treatment**

- limited evidence, depends on pain and interference with intercourse

**Table 24. Treatment of Peyronie's Disease**

Conservative	Medical	Surgical
<ul style="list-style-type: none"> <li>• Reassurance and education</li> <li>• Watchful waiting (spontaneous resolution in up to 50%)</li> </ul>	<ul style="list-style-type: none"> <li>• Vitamin E, colchicine, potassium paraaminobenzoate, and carnitine have all been suggested</li> <li>• Intralesional or topical verapamil</li> </ul>	<ul style="list-style-type: none"> <li>• If stable disease, significant deformity AND failed medical therapy</li> <li>• Incision/excision of plaque</li> <li>• Shortening of less affected side</li> <li>• <math>\pm</math> penile prosthesis</li> </ul>



**Figure 14. Peyronie's disease**



**Mimickers of Peyronie's Disease:**

- Congenital curvature of the penis
- Chordee without hypospadias
- Curvature secondary to penile fracture

### Priapism

**Definition**

- prolonged erection lasting  $>4$  h in the absence of sexual excitement/desire
- tumescence (swelling) of corpora cavernosa with flaccid glans penis (no corpora spongiosum involvement)

**Classification**

- low-flow/ischemic (most common):
  - reduced/absent cavernosal blood flow → hypoxia, acidosis → ischemia
- high-flow/non-ischemic:
  - unregulated arterial flow with normal tissue oxygenation

### Etiology

- primary: up to 50% idiopathic
- secondary:
  - thromboembolic: e.g. sickle cell, thalassemia, total parenteral nutrition, dialysis, leukemia, solid tumours
  - neurogenic: spinal cord injury, autonomic neuropathy
  - traumatic: cavernosal artery laceration, arterio-venous fistula
  - medication: intracavernosal vasoactive drug injection (e.g. triple mix),  $\alpha$ -blockers, anticoagulants, antidepressants, antipsychotics, anxiolytics, PDE-5 inhibitors
  - recreational drugs: cocaine, marijuana, heavy alcohol intake

### Treatment

- treat reversible causes
- high-flow often self-limited, but arterial embolization may be considered
- low-flow:
  1. urgent decompression via needle aspiration
  2. phenylephrine injection into the corpora cavernosa q3-5min (in monitored setting)
  3. shunt creation between cavernosum and spongiosum if no response within 1 h

### Complications

- ED due to corporal fibrosis if treatment delayed
  - 90% risk if >24 h



Ischemic priapism is a urological emergency.



#### Key Differences between Ischemic (I) and Non-Ischemic (NI) Priapism:

Finding	IP	NIP
Rigid corpora cavernosa	U	0
Penile pain	U	0
Abnormal cavernosal blood gases	U	0
CBC abnormalities and hematologic malignancy	S	0
Recent intracavernosal vasoactive drug injection	S	0
Chronic, well-tolerated swelling without full rigidity	0	U
Perineal trauma	0	S

U = Usually present

S = Sometimes present

0 = Seldom present

Source: Guideline on the Management of Priapism. American Urological Association Education and Research, Inc. © 2003.



To prevent paraphimosis, foreskin should always be reduced to normal anatomic position following instrumentation (including following catheterization).



Normal congenital adhesions separate naturally by 3 yr in 90% of uncircumcised boys.



**Erections POINT AND SHOOT**  
parasympathetics = **point**; and  
sympathetics/somatics = **shoot**

## Paraphimosis

### Definition

- foreskin caught behind glans leading to edema → inability to reduce foreskin

### Treatment

- squeeze edema out of the glans with manual pressure (analgesia required)
- pull on foreskin with fingers while pushing on glans with thumbs
- if fails, perform dorsal slit or circumcision
- elective circumcision for definitive treatment (paraphimosis tends to recur)

### Complications

- infection, glans ischemia, gangrene

## Phimosis

### Definition

- inability to retract foreskin over glans penis
- may be caused by balanitis (infection of glans), often due to poor hygiene or congenital

### Treatment

- proper hygiene, topical corticosteroids, dorsal slit, circumcision

### Complications

- balanoposthitis (inflammation of prepuce), paraphimosis, penile cancer

## Erectile Dysfunction (ED)

### Definition

- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

### Physiology

- erection involves the coordination of psychological, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic [dorsal penile/pudendal nerves (S2-4)]
- erection ("POINT"):
  - parasympathetics → release of nitric oxide (NO) → increased cGMP levels within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)

- emission (“SHOOT”):
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
- ejaculation (“SHOOT”)
  - bladder neck closure (sympathetic)
  - spasmodic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
- detumescence:
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

## Classification

**Table 25. Classification of Erectile Dysfunction**

	Psychogenic	Organic
<b>Proportion</b>	10%	90%
<b>Onset</b>	Sudden	Gradual
<b>Frequency</b>	Sporadic	All circumstances
<b>Variation</b>	With partner and circumstance	No
<b>Age</b>	Younger	Older
<b>Organic risk factors (HTN, DM, dyslipidemia)</b>	No organic risk factors	Risk factors present
<b>Nocturnal/AM erection</b>	Present	Absent

## Etiology (“IMPOTENCE”)

- Iatrogenic: pelvic surgery, pelvic radiation
- Mechanical: Peyronie’s, post-priapism
- Psychological: depression, stress, anxiety, PTSD, widower syndrome
- Occlusive vascular: arterial HTN, DM, smoking, hyperlipidemia, PVD, venous (impaired veno-occlusion)
- Trauma: penile/pelvic, bicycling
- Extra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
- Neurogenic: CNS (e.g. Parkinson’s, MS, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
- Chemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anticholinergics, antihistamines, anti-androgens (including 5- $\alpha$  reductase inhibitors), statins, GnRH agonists, illicit drugs
- Endocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

## Diagnosis

- complete hx (include sexual, medical, and psychosocial aspects)
- self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
- focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
- lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
- specialized testing including nocturnal penile tumescence monitoring and evaluation of penile vasculature is usually unnecessary

## Treatment

- can often be managed by family doctor, see sidebar for when to refer
- must fully inform patient/partner of options, benefits and complications
- non-invasive:
  - lifestyle changes (alcohol, smoking), psychological (sexual counseling and education)
  - change precipitating medications
  - treat underlying causes (diabetes, CVD, HTN, endocrinopathies)
- minimally invasive:
  - oral medication (see *Common Medications*, U43)
    - ♦ sildenafil, tadalafil, vardenafil: inhibits PDE-5 to increase intracavernosal cyclic GMP levels
      - all three have similar effectiveness, but tadalafil has certain advantages: earlier onset, longer half-life, no cyanopsia, can be taken on empty or full stomach (others better on empty stomach)
  - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis once erect
  - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra



Penile vascular abnormalities may be a marker of risk for CV disease. Young men with vascular ED have 50x higher risk of having a CV event.



Testosterone deficiency is an uncommon cause of ED.



### When to Consider Referral

#### FAT PEN

Failed medical therapy  
penile Anatomic abnormality  
pelvic/perineal Trauma  
Psychogenic cause  
Endocrinopathy  
vascular/Neurologic assessment



PDE-5 inhibitors are contraindicated in patients on nitrates/nitroglycerin due to severe hypotension.

- invasive:
  - intracavernous vasodilator injection/self-injection
    - ♦ triple therapy (papaverine, phentolamine, PGE1) or PGE1 alone
    - ♦ complications: priapism (overdose), thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) and hematoma
- surgical:
  - penile implant (last resort): malleable or inflatable
  - penile artery reconstruction (in young men with isolated vascular lesion – investigational)



Initial trial of MUSE or intracavernosal injection should be done under medical supervision.

## Premature Ejaculation

### Definition

- occurrence of ejaculation prior to when one or both partners desire it, either before or soon after penetration
- often thought to be due to psychological factors
- primary premature ejaculation
  - never experienced sexual activity without the presence of premature ejaculation
- secondary premature ejaculation
  - the individual once had acceptable ejaculatory control, but now experiences premature ejaculation, not associated with a general medical condition

### Epidemiology

- 3-30% prevalence (self-reporting is consistently higher than clinical prevalence)
- most common sexual dysfunction reported in men 18-30 yr, associated with secondary impotence in men 45-65 yr

### Investigations

- indicated by hx and P/E
- testosterone levels if in conjunction with impotence

### Treatment

- must r/o and treat any associated general medical conditions (e.g. fear of angina)
- referral to psychiatry, couples counseling or sex therapy
- SSRIs or clomipramine, either daily or on-demand dosing
- topical lidocaine and/or prilocaine



**Efficacy and Safety of Fluoxetine, Sertraline, and Clomipramine in Patients with Premature Ejaculation: a Double-blind, Placebo Controlled Study**

*J Urol* 1998;159:425-427

**Purpose:** To compare the efficacy and safety of fluoxetine, sertraline, clomipramine and placebo for premature ejaculation.

**Methods:** 36 men who had intravaginal ejaculation latency <2 min were recruited. Mean age was 44 yr. Patients took each of 3 drugs and the placebo consecutively during a 4 wk period per each agent. Self-reported questionnaires were used to assess efficacy and side effects.

**Results:** The mean intravaginal ejaculation latency time was significantly increased from 46 s with placebo to 2.27 min, 2.30 min, 4.27 min and 5.75 min, with fluoxetine, sertraline and clomipramine, respectively (all  $p < 0.01$ ). Treatment with clomipramine or sertraline caused a greater increase in mean intravaginal ejaculation latency time than fluoxetine or placebo ( $p < 0.01$ ). Patient sexual satisfaction rate after clomipramine treatment was significantly higher ( $p < 0.05$ ) compared to the other agents. Side effect incidence was higher with clomipramine than fluoxetine, sertraline and placebo ( $p < 0.05$ ).

**Conclusions:** Clomipramine has the best efficacy, but sertraline is nearly as effective with a lower incidence of side effects.

## Trauma

- see [Emergency Medicine](#), ER14



## Renal Trauma

### Classification According to Severity

- minor:
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major:
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

### Etiology

- 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

### Clinical Features

- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

### Investigations

- U/A:
  - hematuria: requires workup but degree does not correlate with the severity of injury
- imaging:
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

**Staging (does not necessarily correlate well with clinical status)**

- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: urinary extravasation
- V: shattered kidney or avulsion of pedicle

**Treatment**

- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization:
  - absolute indications:
    - ♦ hemorrhage and hemodynamic instability
  - relative indications
    - ♦ non-viable tissue and major laceration
    - ♦ urinary extravasation
    - ♦ vascular injury
    - ♦ expanding or pulsating peri-renal mass
    - ♦ laparotomy for associated injury
- F/U with U/S or CT before D/C, and at 6 wk

**Complications**

- HTN in 5% of renal trauma

## Bladder Trauma

**Classification**

- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

**Etiology**

- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

**Clinical Features**

- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

**Investigations**

- U/A: gross hematuria in 90%
- imaging (including CT cystogram and post-drainage films for extravasation)

**Treatment**

- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

**Complications**

- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture



## Urethral Injuries

### Etiology

- posterior urethra:
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra:
  - straddle injury can crush bulbar urethra against pubic rami
- other causes:
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture



All patients with suspected urethral injury should undergo RUG.

### Clinical Features

- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder

### Investigations

- must perform RUG or cystoscopy prior to catheterization

### Treatment

- simple contusions:
  - no treatment
- partial urethral disruption:
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment in OR
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption:
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

### Complications

- stricture

## Infertility

### Definition

- failure to conceive after one year of unprotected, properly timed intercourse
- incidence:
  - 15% of all couples
  - ~ 35-40% female, 20% male, 25-30% combined problem

## Female Factors

- see [Gynecology](#), GY22



## Male Factors

### Male Reproduction

- hypothalamic-pituitary-testicular axis (HPTA):
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

## Etiology

- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumour
  - congenital (Klinefelter's triad: small, firm testes, gynecomastia, and azoospermia)
  - post-infectious (epididymo-orchitis, STIs, mumps)
  - uncorrected torsion
  - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery: see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
  - bilateral ejaculatory duct obstruction, epididymal obstructions
  - Kartagener's syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see [Endocrinology](#), E47)
- HPTA (2-3%) e.g. Kallmann's syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery
  - medications (see below)
  - drugs: marijuana, cocaine, tobacco, alcohol
  - increased testicular temperature (sauna, hot baths, tight pants or underwear)
  - chronic disease: e.g. liver, renal
  - unexplained infertility

## History

- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STIs
- surgical: vasectomy, herniorrhaphy orchidopexy, cryptorchidism, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- family hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone,  $\alpha$ -blockers
- social hx: alcohol, tobacco, cocaine
- occupational exposures: radiation, heavy metals

## Physical Exam

- general appearance: sexual development, gynecomastia, obesity
- scrotal exam: size, consistency and nodularity of testicles; palpation of cord; DRE; Valsalva for varicocele

## Investigations

- semen analysis (SA) at least 2 properly obtained specimens over several weeks
- hormonal evaluation:
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
  - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation:
  - chromosomal studies (Klinefelter's syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

## Treatment

- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see [Endocrinology](#), E48)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start  $\alpha$ -adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections



### Male Infertility Factors

#### SPERM COUNT

Systemic factor/Smoking

Psychological illness

Endocrinopathy

Retrograde ejaculation

Medications

Chronic disease

Obstructive

Unexplained

Narcotics

Testicular



### WHO Guidelines

#### Normal Semen Values

- Volume: 2-5 mL
- Concentration: >15 million sperm/mL
- Morphology: 30% normal forms
- Motility: >40% adequate forward progression
- Liquefaction: complete in 20 min
- pH: 7.2-7.8
- WBC: <10/HPF or <10<sup>6</sup> WBC/mL semen



Mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene is associated with congenital bilateral absence of vas deferens and epididymal cysts, even if patient manifests no symptoms of CF.



### Common Terminology on SA:

- Teratospermia: Abnormal morphology
- Asthenospermia: Abnormal motility
- Oligospermia: Decreased sperm count
- Azoospermia: Absent sperm in semen
- Mixed types, i.e. oligoasthenospermia



The majority of men with infertility will show oligospermia and asthenospermia on SA.



- surgical
  - varicocele (if indicated)
  - vasovasostomy (vasectomy reversal)
  - epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART):
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - in vitro fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

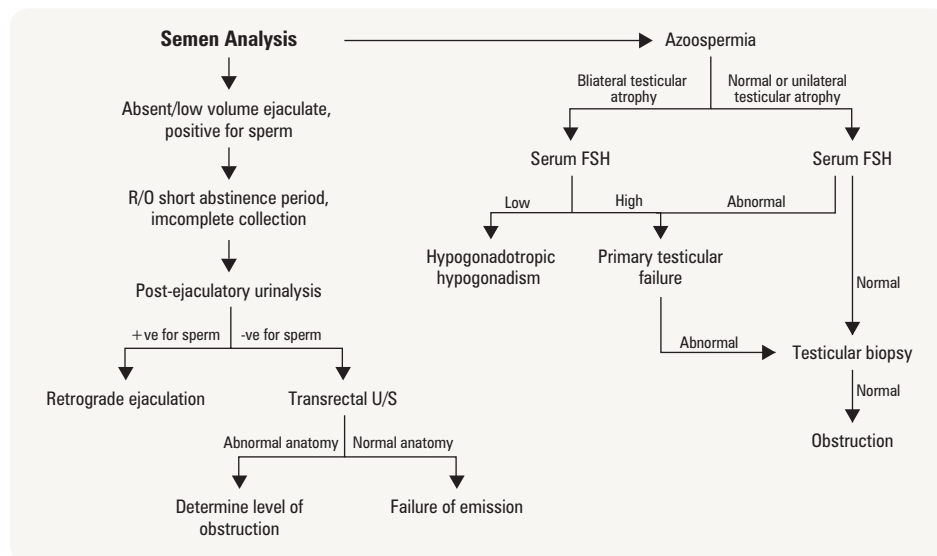


Figure 15. Infertility workup

## Pediatric Urology

### Congenital Abnormalities

- not uncommon; 1/200 have congenital abnormalities of the GU tract
- six common presentations of congenital urological abnormalities:

#### 1. ANTENATAL HYDRONEPHROSIS

##### Epidemiology

- 1-5% fetal U/S, detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

##### Differential Diagnosis

- UPJ or UVJ obstruction
- multi-cystic dysplastic kidney
- VUR
- PUVs (only in boys)
- duplication anomalies
- ureterocele
- ectopic ureter

##### Treatment

- antenatal in utero intervention rarely indicated unless evidence of PUVs with oligohydramnios



Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life.

#### 2. POSTERIOR URETHRAL VALVES (PUV)

##### Epidemiology

- the most common congenital obstructive urethral lesion in male infants

### Pathophysiology

- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

### Clinical Presentation

- dependent on age:
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive
  - toddlers: UTIs or voiding dysfunction
  - school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

### Investigations

- most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened bladder, dilated posterior urethra ("keyhole sign"), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

### Treatment

- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

## 3. URETEROPELVIC JUNCTION (UPJ) OBSTRUCTION

### Etiology

- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, stenosis, strictures, aberrant blood vessels
- can be secondary to tumour, stone, etc.

### Epidemiology

- the most common congenital defect of the ureter
- M:F = 2:1
- up to 40% bilateral, which may be associated with worse prognosis

### Clinical Presentation

- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
  - in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl's crisis)

### Investigations

- antenatal U/S most common, Doppler U/S (rare), IVP (rare), and renal scan ± furosemide

### Treatment

- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

## 4. VESICoureTERAL REFLUX (VUR)

### Definition

- retrograde passage of urine from the bladder, through the ureterovesicular junction (UVJ), into the ureter

### Classification

- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neurogenic) bladder obstruction

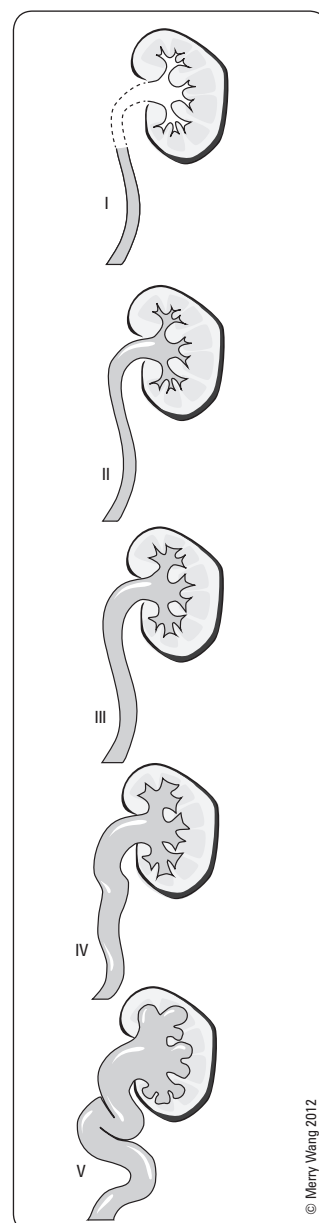
### Epidemiology

- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition



#### VUR Grading (based on cystogram)

- **Grade I:** ureters only fill
- **Grade II:** ureters and pelvis fill
- **Grade III:** ureters and pelvis fill with some dilatation
- **Grade IV:** ureters, pelvis, and calyces fill with significant dilatation
- **Grade V:** ureters, pelvis, and calyces fill with major dilatation and tortuosity



**Figure 16. VUR grading**  
(based on cystogram)

### Investigations

- focused hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for signs of infection (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to high incidence of renal scarring
  - height, weight, blood pressure
  - Cr
  - U/A, C&S
  - renal U/S
  - DMSA renal scan if at high risk (greater sensitivity than U/S but entails radiation exposure)
  - family screening is controversial

### Treatment

- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment and monitoring
- medical treatment: long-term ABx prophylaxis at half the treatment dose for half the treatment time (TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
- surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (Deflux® or Macroplastique®)
  - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

## 5. HYPOSPADIAS

### Definition

- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream or infertility

### Epidemiology

- very common; 1/300 live male births
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia

### Treatment

- early surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

## 6. EPISPADIAS-EXSTROPHY COMPLEX

### Definition

- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  - bladder exstrophy: congenital absence of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  - cloacal exstrophy:
    - ♦ exposed bladder and bowel with imperforate anus
    - ♦ associated with spina bifida in >50%
  - epispadias (least severe)
    - ♦ urethra opens on dorsal aspect of the penis

### Etiology

- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

### Epidemiology

- rare: incidence 1/30,000, 3:1 male to female predominance
- high morbidity → incontinence, infertility, reflux

### Treatment

- surgical correction at birth
- later corrections for incontinence, VUR, and bladder capacity may be needed



Defer circumcision in patients with hypospadias.

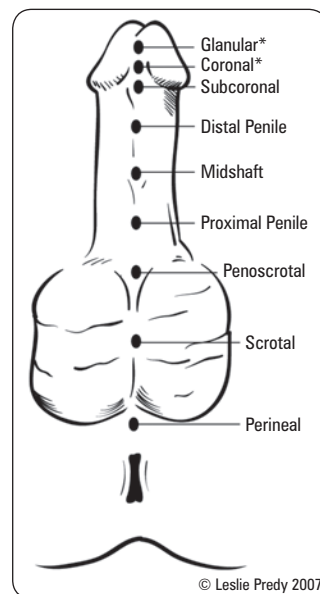


Figure 17. Classification of hypospadias (\*account for 75%)

## Nephroblastoma (Wilms' Tumour)

### Etiology

- arises from abnormal proliferation of metanephric blastema

### Epidemiology

- 5% of all childhood cancers, 5% bilateral
- most common primary malignant renal tumour of childhood
- average age of incidence is 3 yr

### Clinical Features

- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness
- microscopic hematuria
- nausea/vomiting

### Treatment

- always investigate contralateral kidney
- unilateral disease: radical nephrectomy ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

### Prognosis

- 5-yr survival 80%

## Cryptorchidism/Ectopic Testes

### Definition

- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- ectopic testis (testis found outside its normal path of descent) is most commonly located within a superficial pouch between the external oblique fascia and Scarpa's fascia (Denis Browne pouch)
- differential diagnosis:
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

### Epidemiology

- 2.7% of full term newborns
- 0.7%-0.8% at 1 yr old

### Treatment

- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

### Prognosis

- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility
  - paternity rates: 53%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intraabdominal > inguinal
  - surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)



#### Normal Testicular Development and Descent in Utero

**2nd month:** Testicle begins to form.

**4th month:** Begins to take on its normal appearance and migrates from its origin. at the kidney to the internal inguinal ring.

**7th month:** The testis, surrounded in peritoneal covering, begins to descend through the internal ring, inguinal canal and external ring to terminate in the scrotum.

## Disorders of Sexual Differentiation (DSD)

### Definition

- formerly known as intersex disorders
- abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females
- considered a social emergency

### Classification

1. 46 XY DSD
  - defect in testicular synthesis of androgens
  - androgen resistance in target tissues
  - palpable gonad



2. 46 XX DSD
  - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
  - undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)
3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
  - presence of Y chromosome → partial testis determination to varying degrees

### Diagnosis

- thorough family hx noting any consanguinity
- maternal hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
- P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
- laboratory tests:
  - plasma 17-OH-progesterone (after 36 h of life) → increased in 21-hydroxylase deficiency (CAH)
  - plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  - basal adrenal steroid levels
  - serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/d for 4 d)
  - serum electrolytes
  - chromosomal evaluation including sex karyotype
- U/S of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and genitography of urogenital sinus

### Treatment

- steroid supplementation as indicated (e.g. CAH)
- sex assignment after extensive family consultation
  - must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
- reconstruction of external genitalia between 6 and 12 mo
- long-term psychological guidance and support for both patient and family



#### Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men

*Cochrane DB Syst Rev* 2009;2:CD003362

**Purpose:** To evaluate the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.

**Methods:** The analyzed data is from three randomized controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa.

**Results:** Medical male circumcision reduces the acquisition of HIV by heterosexual men (38%-66% over 24 mo).



#### Circumcision Status and Risk of HIV and Sexually Transmitted Infections among Men who have Sex with Men: A Meta-analysis

*JAMA* 2008;300:1674-1684

**Purpose:** To describe the association between male circumcision and HIV infection and other sexually transmitted infections (STIs) among men who have sex with men (MSM).

**Methods:** Meta-analysis of 15 studies (n = 53 567). The associations between circumcision and HIV-positive and STIs were not statistically significant. Male circumcision had a protective association with HIV in studies of MSM conducted before the introduction of highly active antiretroviral therapy.

**Conclusions:** There is insufficient evidence to support that male circumcision protects against HIV infection or other STIs.



#### Canadian Pediatric Society Position Statement: Neonatal Circumcision Revisited

*CMAJ* 1996;154:769-780

**Objective:** To assist physicians in providing guidance to parents regarding neonatal circumcision.

**Methods:** The literature on circumcision was reviewed by the Fetus and Newborn Committee of the Canadian Paediatric Society.

**Recommendation:** Circumcision of newborns should not be routinely performed. There is inadequate information to recommend circumcision as a public health measure to prevent penile cancer and HIV transmission.



#### Male Circumcision

*Pediatrics* 2012;130:e756-e785

**Study:** Guidelines by the American Academy of Pediatrics (AAP)

**Recommendations:** The American Academy of Pediatrics radically changed their position on male circumcision in 2012. The report from the AAP now states that the preventative health benefits outweigh the risks of the procedure and that the procedure is well-tolerated with adequate pain management and sterility. Stated benefits include the prevention of urinary tract infection, penile cancer, transmission of some sexually transmitted infections, including HIV. There is believed to be no effect on penile sexual function, sensitivity or sexual satisfaction. Acute complications are rare and more common if the procedure is done by an untrained provider.

**Note:** The Canadian Pediatric Society (CPS) has not yet updated their position on male circumcision since 1996, which stated that the CPS is opposed to routine circumcision. A new statement is expected soon.

## Circumcision

### Definition

- removal of some or all of the foreskin from the penis

### Epidemiology

- 30% worldwide
- frequency varies depending on geographic location, religious affiliation, socioeconomic classification

### Medical Indications

- phimosis and recurrent paraphimosis
- recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
- balanitis xerotica obliterans or other chronic inflammatory conditions

### Contraindications

- unstable or sick infant
- congenital genital abnormalities (hypospadias)
- family hx of bleeding disorders warrants laboratory investigation prior to circumcision

### Complications

- bleeding
- infection
- penile entrapment, skin bridges
- fistula
- glans injury
- penile sensation deficits

## Enuresis

- see [Pediatrics](#), P9



## Selected Urological Procedures



### Bladder Catheterization

- catheter size measured by the French (Fr) scale – circumference in mm
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 16-18 Fr)
- should be removed as soon as possible

#### Continuous Catheterization

- indications:
  - accurate monitoring of U/O
  - relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  - temporary therapy for urinary incontinence
  - perineal wounds
  - clot prevention (24-28 Fr) for CBI
  - post-operative

#### Alternatives to Continuous Catheterization

- intermittent catheterization:
  - PVR measurement
  - to obtain sterile diagnostic specimens for U/A, urine C&S
  - management of neurogenic bladder or chronic urinary retention
- condom catheter
- suprapubic catheter

#### Causes of Difficult Catheterizations and Treatment

- patient discomfort → use sufficient lubrication ( $\pm$  xylocaine)
- collapsing catheter → lubrication as above  $\pm$  firmer catheter (silastic catheter)
- meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
- BPH → use coude catheter as angled tip can help navigate around prostate
- urethral disruption/obstruction → filiform and followers or suprapubic catheterization
- anxious patient → anxiolytic medication

#### Complications of Catheterization

- infection: UTI
- meatal/urethral trauma

#### Contraindications

- urethral trauma: blood at the meatus of the urethra, scrotal hematoma, pelvic fracture, and/or high riding prostate

## Cystoscopy

#### Objective

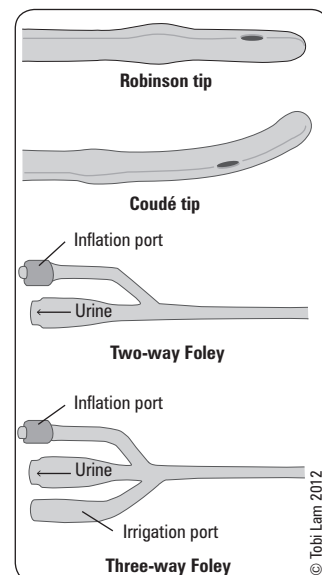
- endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
- scopes can be flexible or rigid

#### Indications

- gross hematuria
- LUTS (storage or voiding)
- urethral and bladder neck strictures
- bladder stones
- bladder tumour surveillance
- evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

#### Complications

- during procedure
  - bleeding
  - anesthetic-related
  - perforation (rare)
- post-procedure (short-term)
  - infections, e.g. epididymo-orchitis (rare)
  - urinary retention
- post-procedure (long-term)
  - stricture



**Figure 18. Transurethral (Foley) catheters**

## Radical Prostatectomy (RP)

### Objective

- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also ligated or removed

### Indications

- treatment for localized prostate cancer

### Complications

- immediate (intraoperative):
  - blood loss
  - rectal injury
  - ureteral injury (extremely rare)
- perioperative:
  - lymphocele formation
- late:
  - moderate to severe urinary incontinence (3-10%)
  - mild urinary incontinence (20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)



**Retropubic, Laparoscopic, and Robot-Assisted Radical Prostatectomy: A Critical Review of Outcomes Reported by High-Volume Centers**  
*J Endourology* 2010;24:2003-2015

**Study:** A systematic review to compare perioperative outcomes, positive surgical margin (PSM) rates, and functional outcomes in retropubic radical prostatectomy (RRP) laparoscopic RP (LRP) and robot-assisted radical prostatectomy (RARP).

**Methods:** Medline database was searched. Weighted means (based on number of participants in each study) were calculated for all outcomes.

**Results:** 58 articles were reviewed. LRP and RARP were associated with better perioperative outcomes compared to RRP. RRP, LRP and RARP had similar post-operative complication rates ranging from 10.3-10.98%. RARP had a lower overall PSM rate than LRP and RRP. RARP had the highest continence rate and mean potency rates.

**Conclusion:** In high-volume centers, RRP, LRP and RARP are safe options for treating patients with localized prostate cancer. LRP and RARP are associated with better peri-operative outcomes and RARP showed lower PSM rates, higher potency and continence compared to RRP and LRP.

## Transurethral Resection of the Prostate (TURP)

### Objective

- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination

### Indications

- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

### Complications

- acute:
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called "post-TURP syndrome")
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinusoids, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic:
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture

## Extracorporeal Shock Wave Lithotripsy (ESWL)

### Objective

- to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
- shockwaves are generated and focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

### Indications

- potential first-line therapy for renal and ureteral calculi <2.5 cm
- individuals with calculi in solitary kidney
- individuals with HTN, DM or renal insufficiency
- \*patient preference and wait-times play a large role in stone management

### Contraindications

- acute UTI or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- obstruction distal to stone

### Complications

- bacteriuria
- bacteremia
- post-procedure hematuria
- ureteric obstruction (by stone fragments)
- peri-nephric hematoma



#### A Comparison of Treatment Modalities for Renal Calculi Between 100 and 300 mm<sup>2</sup>: Are Shockwave Lithotripsy, Ureteroscopy, and Percutaneous Nephrolithotomy Equivalent?

*J Endourol* 2011;25:481-485

**Purpose:** To describe the outcomes of a series of patients who underwent shockwave lithotripsy (SWL), ureteroscopy (URS) or percutaneous nephrolithotomy (PCNL).

**Methods:** Patients treated for intermediate-sized upper tract calculi (100-300 mm<sup>2</sup>) at a single tertiary centre were included. Demographic and clinical data were collected from a prospectively maintained database.

**Results:** Of a 137 patients, 38.7%, 29.9%, and 31.4% were treated with SWL, URS, and PCNL, respectively. Stone-free rate (95.3%) and single treatment success rate (95.3%) were highest for PCNL compared to SWL and URS ( $p < 0.001$ ). When allowing for up to two SWL treatments, success rates became equivalent for the three treatment groups ( $p = 0.66$ ). Auxiliary treatments were more frequent after SWL compared to URS and PCNL. Clavien grade complications did not differ between the three groups.

**Conclusion:** Up to two SWL treatments have equivalent success rate as compared to URS and PCNL. Hence, multiple SWL treatments may be a reasonable therapeutic option for patients who prefer SWL or who are not good candidates for alternative therapies.

## Common Medications

**Table 26. Erectile Dysfunction Medications**

Drug	Class	Mechanism	Adverse Effects
sildenafil tadalafil vardenafil (for use when some erection present)	Phosphodiesterase 5 inhibitor	Selective inhibition of PDE5 (enzyme which degrades cGMP) Leads to sinusoidal smooth muscle relaxation and erection	Severe hypotension (very rare) Contraindicated if hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease) Contraindicated with nitrates
alprostadil (MUSE), PGE <sub>1</sub> + phentolamine + papaverine mixture	Prostaglandin E <sub>1</sub>	Activation of cAMP, relaxing sinusoidal smooth muscle Local release (capsule inserted into urethra)	Penile pain Presyncope
alprostadil, papaverine (intracavernosal injection)	See above	See above	Thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) Painful erection Hematoma Contraindicated if hx of priapism, or in conditions predisposing to priapism
triple therapy also used: papaverine, phentolamine, PGE <sub>1</sub>			

**Table 27. Benign Prostatic Hyperplasia Medications**

Drug	Class	Mechanism	Adverse Effects
terazosin doxazosin	$\alpha_1$ blockers	$\alpha$ -adrenergic antagonists reduce stromal smooth muscle tone Reduce dynamic component of bladder outlet obstruction	Presyncope Leg edema Retrograde ejaculation
tamsulosin alfuzosin	$\alpha_{1A}$ selective		Headache Asthenia Nasal congestion
finasteride dutasteride	5 $\alpha$ -reductase inhibitor	Blocks conversion of testosterone to DHT Reduces static component of bladder outlet obstruction Reduces prostatic volume	Sexual dysfunction PSA decreases

**Table 28. Prostatic Carcinoma Medications (N>0, M>0)**

Drug	Class	Mechanism	Adverse Effects
leuprolide, goserelin	GnRH agonist	Initially stimulates LH, increasing testosterone and causing "flare" (initially increases bone pain) Later causes low testosterone	Hot flashes Headache Decreased libido
*diethylstilbestrol (DES)	Estrogens	Inhibit LH and cytotoxic effect on tumour cells	Increased risk of cardiovascular events (no longer available commercially in North America)
*cyproterone acetate	Steroidal antiandrogen	Competes with DHT for intracellular receptors: 1. Prevent flare produced by GnRH agonist 2. Use for complete androgen blockade 3. May preserve potency	
flutamide, bicalutamide	Non-steroidal antiandrogen	As above	Hepatotoxic: AST/ALT monitoring
*ketoconazole, spironolactone	Steroidogenesis inhibitors	Blocks multiple enzymes in steroid pathway, including adrenal androgens	GI symptoms Hyperkalemia Gynecomastia

\*Very rarely used

**Table 29. Continence Agents and Overactive Bladder Medications**

Drug	Class	Mechanism	Indication	Adverse Effects
oxybutynin	Antispasmodic	Inhibits action of ACh on smooth muscle Decreases frequency of uninhibited detrusor contraction Diminishes initial urge to void	Urge incontinence + urgency + frequency	Dry mouth Blurred vision Constipation Supraventricular tachycardia
oxybutynin, tolterodine, trospium, solifenacin, darifenacin	Anticholinergic	Muscarinic receptor antagonist Selective for bladder Increases bladder volume Decreases detrusor pressure	Urge incontinence + urgency + frequency	As above
imipramine	Tricyclic antidepressant	Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation	Stress and urge incontinence	As above Weight gain Orthostatic hypotension Prolonged PR interval

Note: All anti-cholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long acting formulations are lacking.

## References

### General Information

American Urological Association. Available from: <http://www.auanet.org/guidelines/>.  
Canadian Urological Association. Available from: [http://www.cua.org/guidelines\\_e.asp](http://www.cua.org/guidelines_e.asp).  
Ferri F. Practical guide to the care of the medical patient, 6th ed. St. Louis: Mosby, 2006.  
Goldman L, Ausiello D. Cecil textbook of medicine, 23rd ed. Philadelphia: WB Saunders, 2007.  
Macfarlane MT. House officer series: urology, 3rd ed. Philadelphia: Lippincott, 2001.  
Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JPW, Lue TF, Nehra A, Sharlip ID. Guideline on the management of priapism. American Urological Association Education and Research, Inc. ©2003. Available from: <http://www.auanet.org/education/guidelines/priapism.cfm>.  
Tanagho EA, McAninch JW. Smith's general urology, 17th ed. New York: McGraw-Hill, 2007.  
Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. Campbell's urology, 10th ed. Philadelphia: WB Saunders, 2011.  
Wieder JA. Pocket guide to urology, 4th ed. Oakland: Wieder, 2010.

### Common Presenting Problems

Bremner JD, Sadovsky R. Evaluation of dysuria in adults. *Am Fam Phys* 2002;65:1589-1597.  
Cohen RA, Brown RS. Microscopic hematuria. *NEJM* 2003;348:2330-2338.  
Morton AR, Ilescu EA, Wilson JWL. Nephrology: investigation and treatment of recurrent kidney stones. *CMAJ* 2002;166:213-218.  
Teichman JMH. Acute renal colic from ureteral calculus. *NEJM* 2004;350:684-693.

### Benign Renal Neoplasm

Israel GM, Bosniak MA. An update of Bosniak renal cyst classification system, *Urology* 2005;66:484-488.

### Urological Emergencies

Galejs LE. Diagnosis and treatment of the acute scrotum. *Am Fam Phys* 1999;5:817-824.

### Medications

Bill-Axelsson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, Nordling S, Häggman M, Andersson SO, Bratell S, Spångberg A, Palmgren J, Steineck G, Adami HO, Johansson JE, SPCG-4 Investigators. Radical prostatectomy versus watchful waiting in early prostate cancer. *NEJM* 2011;364:1708-1717.  
Compendium of Pharmaceuticals and Specialties. Available from: <http://www.e-therapeutics.ca>.  
Micromedex health care series. Available from: <http://www.micromedex.com>.  
Rini B, Halabi S, Rosenberg J, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol* 2008;26:5422-5428.

### EBM

Bill-Axelsson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *NEJM* 2011;364:1708-1717.  
Coelho RF, Rocco B, Patel MB, Orvieto MA, Chauhan S, Ficarra V, Melegari S, Palmer KJ, Patel VR. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. *J Endourol* 2010;24:2003-2015.  
Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *NEJM* 2007;356:125-134.  
Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *NEJM* 2003;349:859-866.  
Ilic D, O'Connor D, Green S, et al. Screening for prostate cancer. *Cochrane DB Syst Rev* 2013;1:CD004720.  
Kim SC, Seo KK. Efficacy and safety of fluoxetine, sertraline and clomipramine in patients with premature ejaculation: a double-blind, placebo controlled study. *J Urol* 1998;159:425-427.  
McDonnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *NEJM* 2003;349:2387-2398.  
Millett GA, Flores SA, Marks G, Reed JB, Herbst JH. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. *JAMA* 2008;300:1674-1684.  
Outerbridge E, Canadian Paediatric Society, Fetus and Newborn Committee. position statement: neonatal circumcision revisited. *Can Med Assoc J* 1996;154:769-780.  
Parsons JK, Hergan LA, Sakamoto K, Lakin C. Efficacy of alpha-blockers for the treatment of ureteral stones. *J Urol* 2007;177:983-987.  
Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *NEJM* 2009;360:1320-1328.  
Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane DB Syst Rev* 2009;2:CD003362.  
Wiesenthal JD, Ghiculete D, D'A Honey RJ, Pace KT. A comparison of treatment modalities for renal calculi between 100 and 300 mm<sup>2</sup>: are shockwave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy equivalent? *J Endourol* 2011;25:481-485.  
Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *NEJM* 2012;367:203-213.



# Index

3,6,9 Rule; MI13  
 4:2:1 Rule; A13  
 $\alpha$ -1-Antitrypsin Deficiency; R9  
 $\alpha$ -Thalassemia; H19  
 $\beta$ -hCG; GY8, OB3  
 $\beta$ -Thalassemia; H18

## A

### Abdominal

Air; MI12  
 Anatomy; MI11  
 Distention; G4  
 Imaging; MI27  
 Incisions; GS2  
 Mass; GS5, P40  
 Pain; ER19, FM13, G4, GS4  
 Pain, Pediatric; ER58, P38  
 X-Ray; MI10  
 Abducens Nerve; N9  
 Abnormal Uterine Bleeding; GY6, GY14  
 Abortion; ELOAM15, ER40  
 Induced; OB11  
   Spontaneous; OB23  
 Abrasion; ER18  
 Abruptio Placentae; OB25, OB27  
 Abscess, Cerebral; NS15  
 Abscess Drainage; MI29  
 Abscess, Intra-abdominal; GS12  
 Absence Epilepsy; P87  
 Absolute Risk Increase/Reduction; PH10  
 Abuse and Neglect, Pediatric; P14  
 Abuse, Elder; FM28  
 Acanthosis Nigricans; D40  
 Accelerated Idioventricular Rhythm; C19  
 Accessory Nerve; N11  
 Accuracy; PH15  
 Acetaminophen; A18  
 Acetaminophen Liver Damage; G32  
 Acetylcholine; CP13  
 Achalasia; G9  
 Achilles Tendonitis; OR36  
 Achilles Tendon Rupture; OR37  
 Acid-Base Disorders; NP14, R5  
 Acid-Base Status; R5  
 Acne; D11  
 Acne, Neonatal; P78  
 Acne Vulgaris; FM45  
 Acoustic Neuroma; NS14, OT12, OT14  
 Acoustic Stapedial Reflexes; OT11  
 Acromioclavicular Joint Pathology; OR14  
 Actinic Keratosis; D7, D32  
 Activated Charcoal; ER51  
 Acute Chest Syndrome; H19  
 Acute Coronary Syndromes; C24  
 Acute Disseminated Encephalomyelitis; P91  
 Acute Fatty Liver of Pregnancy; OB19  
 Acute Kidney Injury; NP33  
 Acute Liver Failure; G36  
 Acute Lymphoblastic Leukemia; H41  
 Acute Myeloid Leukemia; H35, H42  
 Acute Otitis Media; OT38, P55  
 Acute Renal Failure; NP33  
 Acute Respiratory Distress Syndrome; R26  
 Acute Stress Disorder; PS17  
 Acute Tubular Necrosis; NP27  
 Addison's Disease; E35

Adenocarcinoma; GS14  
 Adenoidectomy; OT41  
 Adenoid Hypertrophy; OT40  
 Adenoma, Toxic; E25  
 Adenomyosis; GY17  
 ADHD; PS37  
 Adherence; PH10  
 Adie's Tonic Pupil; OP31, OP32  
 Adjustment Disorder; PS18  
 Adolescent Medicine; P15  
 Adrenal Mass; MI18  
 Adrenal Medications; E55  
 Adrenergic Receptors; C55  
 Adrenocortical Hormones; E29  
 Adrenocortical Insufficiency; E35  
 Adrenocorticotropin Hormone; E29  
 Adult Onset Still's Disease; RH28  
 Adult Polycystic Kidney Disease; NP31  
 Advanced Cardiac Life Support (ACLS)  
   Guidelines; A28  
 Advanced Reproductive Technologies; ELOAM14  
 Adverse Drug Reactions; CP10  
 Adverse Event; ELOAM3  
 Adynamic Ileus; MI12  
 Aesthetic Surgery; PL33  
 Afferent Loop Syndrome; GS21  
 Age-Related Macular Degeneration; OP26  
 Age Standardized Rate; PH7  
 Agnosia; N22  
 Agonists Drugs; CP8  
 Agranulocytosis; H10  
 AIDS; ID41, P57  
 Air Contaminants; PH21  
 Airspace Disease; MI6  
 Airway; ER50  
   Anatomy; A7  
   Difficult; A9  
   Injuries; ER12  
   Management; A7  
   Obstruction; ER11, OT44  
   Problems in Children; OT43  
   Support; A8  
 Albumin; G28  
 Alcohol; FM12  
   Abuse/Dependence; PS22  
   Intoxication; ER48  
   Withdrawal; PS22  
   Withdrawal Symptoms; ER48  
 Alcoholic Liver Disease; G34  
 Aldosterone; E29, NP13  
 Alkaline Reflux Gastritis; GS20  
 Allen's Test; PL22  
 Allergic Granulomatosis and Angiitis; R20  
 Allergic Reaction; ER30  
 Allergic Rhinitis; OT23  
 Allylamines; ID53  
 Alopecia; D37  
 Altered Sensation; N8  
 Alzheimer's Disease; N19, PS20  
 Amaurosis Fugax; OP37  
 Ambiguous Genitalia; P30  
 Amblyopia; OP40  
 Amenorrhea; FM14, GY12  
 American Society of Anesthesiology (ASA)  
   Classification; A3  
 Aminoglycosides; ID46  
 Amnesia; N22, PS27  
 Amniocentesis; OB7  
 Amniotic Fluid Embolus; OB45

Amniotomy; OB37  
 Amoebas; ID31  
 Amphetamines Dependence/Abuse; PS25  
 Amsterdam Criteria; GS34  
 Amylase; G44  
 Amyloid; H47  
 Amyloidosis; NP23  
 Amyotrophic Lateral Sclerosis; N30  
 Anagen Effluvium; D38  
 Anal Fissures; GS38  
 Analgesics; A18  
   Nephropathies; NP28  
 Anal Neoplasms; GS41  
 Analysis of Variance; PH15  
 Anaphylaxis; ER30  
 ANCA Associated Vasculitis; NP24  
 Androgen; E30  
   Regulation; E47  
 Anemia; H5, P46  
   Aplastic; H16  
   Autoimmune Hemolytic; H21  
   Chronic Disease; H15, P48  
   Folate during Pregnancy; OB13  
   Hemolytic; H17  
   Iron Deficiency; G26, H14, P47  
   Iron during Pregnancy; OB13  
   Macrocytic; H22  
   Microangiopathic Hemolytic; H21  
   Microcytic; H12  
   Normocytic; H16  
   Pernicious; H23  
   Physiologic; P47  
   Sideroblastic; H15  
 Anesthesia; A2  
   Epidural; A20  
   Induction Agents; A6  
   Local; A21  
   Monitoring; A5  
   Obstetrical; A22  
   Pediatric; A23  
   Spinal; A20  
   Topical; A22  
 Aneurysmal Bone Cyst; OR43  
 Aneurysm  
   Aortic; C48  
   Intracranial; NS21  
 Angelman Syndrome; P44  
 Angina, Chronic Stable; C22  
 Angina, Variant; C23  
 Angiodysplasia; GS36  
 Angioedema; D41  
 Angiography; C11, MI28  
 Angiomatous Lesions; P78  
 Angiomyolipoma; U20  
 Angle-Closure Glaucoma; OP5  
 Anisocoria; OP30  
 Anisometropia; OP9  
 Ankle Fracture; OR35  
 Ankle Ligamentous Injuries; OR35  
 Ankylosing Spondylitis; RH21  
 Ann Arbor System; H42  
 Anorectal Abscess; GS39  
 Anorexia Nervosa; PS29  
 Antagonists Drugs; CP8  
 Antenatal Hydronephrosis; U36  
 Antepartum Hemorrhage; OB25  
 Anterior Chamber Depth Test; OP6  
 Anterior Ischemic Optic Neuropathy; N11  
 Antiarrhythmics; C55

Antibiotics; FM53, ID46, ID47  
 Anticholinergic Agents; PS44  
 Anticoagulant Therapy; H55  
 Anti-Coagulant Therapy; N44  
 Antidepressants; PS44  
 Antidiuretic Hormone; E19  
 Antidotes; ER50, ER53  
 Antiepileptic Drugs; N16  
 Antifungals; ID53  
 Anti-Helminthics; ID55  
 Antihyperglycemic Agents; E8  
 Antimalarials; ID54  
 Anti-Metabolite Antibiotics; ID50  
 Antimicrobials; FM53  
 Anti-Mycobacterials; ID51  
 Antiparasitics; ID54  
 Antiparkinsonian Agents; PS44  
 Antiphospholipid Antibody Syndrome; H34, RH12  
 Antiplatelet Therapy; H54, N44  
 Anti-Protozoal; ID55  
 Antipsychotics; PS41  
 Antisocial Personality Disorder; PS32  
 Antithrombin Deficiency; H34  
 Antivirals; ID51  
 Anuria; GS10  
 Anxiety; FM15  
 Anxiety Disorders; PS13  
 Anxiety Disorders, Pediatric; PS34  
 Anxiolytics; PS48  
 Aortic Disease; C47  
 Aortic Dissection; C47  
 Aortic Regurgitation; C39  
 Aortic Stenosis; C39, P18  
 Aortic Tear; ER12  
 Aortoenteric Fistula; G25  
 Apgar Score; P67  
 Aphasia; N21  
 Aplastic Anemia; H16  
 Apnea, Neonatal; P69  
 Apnea, Sleep; R31  
 Apparent Life-Threatening Events; P14  
 Appendicitis; GS28, MI15, P39  
 Apprehension Test; OR11  
 Apraxia; N22  
 Apt Test; OB27  
 Aqueous Flare; OP7  
 Arcus Senilis; OP19  
 Argyll-Robertson Pupil; OP31, OP33  
 Arrhythmias; C12, ER31  
 Arterial Blood Gases; R5  
 Arterial Insufficiency; C44  
 Arterial Occlusion; C44  
 Arterial Ulcers; PL15  
 Arteries; GS3  
 Arteriovenous Malformations; NS23  
 Arthritis; MI23, RH3  
   Degenerative; RH5  
   Enteropathic; RH23  
   Hip; OR27  
   Juvenile Idiopathic; P98  
   Pediatric; P98  
   Psoriatic; RH23  
   Reactive; RH23  
   Rheumatoid; RH8  
   Septic; ID15, RH5  
 Articular Cartilage Defects; OR9  
 Asbestos; MI9  
 Asbestosis; R15  
 Asbestos-Related Pleural Disease; R24  
*Ascaris lumbricoides*; ID34  
 Ascending Cholangitis; G43  
 Ascites; G4, G39  
 ASIA Score; NS28  
 Aspect Score; N44  
 Asperger's Disorder; PS36

*Aspergillus spp.*; ID30  
 Aspiration; OT44  
 Asplenia; ID39, P48  
 Asthma; ER30, ER57, FM16, P94, R6  
 Astigmatism; OP9  
 Astrocytoma; NS13  
 Ataxia; N28  
 Atelectasis; GS10, MI6  
 Atheroembolic Renal Disease; NP18  
 Atherosclerosis; C22, NP29  
 Athlete's Foot; D27  
 Atopic Dermatitis; FM45  
 Atresia, Intestinal; GS63  
 Atrial Fibrillation; C16, ER32  
 Atrial Flutter; C16  
 Atrial Septal Defect; P17  
 Atrophic Vaginitis; GY25  
 Atrophy; N30  
 Attachment Models; PS33  
 Attention Deficit Hyperactivity Disorder; PS37  
 Attributable Risk; PH9  
 Audiometry  
   Impedance; OT11  
   Pure Tone; OT9  
   Speech; OT10  
 Auditory Brainstem Response; OT11  
 Auer Rods; H4  
 Aural Rehabilitation; OT12  
 Autistic Disorder; PS36  
 Autoantibodies in Rheumatic Diseases; RH7  
 Autoimmune Hemolytic Anemia; H21  
 Autoimmune Inner Ear Disease; OT19  
 Autoimmune Thrombocytopenia; P70  
 Autonomic Dysreflexia; U11  
 Autonomic Neuropathy; NP29  
 Autonomic Pharmacology; CP12  
 Autonomy; ELOAM2  
 Autosomal Recessive Polycystic Kidney Disease; NP32  
 Avascular Necrosis; OR6  
 AV Conduction Blocks; C14, ER31  
 AV Nodal Re-Entrant Tachycardia; C18  
 Avoidant Personality Disorder; PS32  
 AV Re-Entrant Tachycardia; C19  
 Axonotmesis; NS29

## B

Babinski Reflex; N2  
 Back Pain; FM41, NS24, OR23, RH22  
 Bacterial Tracheitis; ER57, P92  
 Bacterial Vaginosis; GY25  
 Bacteriology; ID2  
 Bado Classification; OR18  
 Balloon Angioplasty; C28  
 Bankart Lesion; OR11  
 Bariatric Surgery; GS20  
 Barium; MI3  
 Barium Enema/Swallow; MI13  
 Barlow's Test; OR40  
 Barrett's Esophagus; G7  
 Bartholin Gland Abscess; GY29  
 Bartholinitis; GY29  
 Basal Cell Carcinoma; D33, PL5  
 Basal Ganglia; N24  
 Basal Skull Fracture; PL29  
 Battle's Sign; N2  
 B-Cell Lymphoma; H44  
 B-Cell Malignant Proliferation; H46  
 Becker's Nevus; D8  
 Beck's Triad; C43  
 Beckwith-Wiedemann Syndrome; P52  
 Bed Bugs; D28

Beers Criteria; GM14  
 Bee Stings; ER47  
 Behaviour Change; PH6  
 Behaviour Therapy; PS40  
 Bell's Palsy; N31, OT22  
 Bence-Jones protein; H47  
 Beneficence; ELOAM3  
 Benign Focal Epilepsy of Childhood; P87  
 Benign Paroxysmal Positional Vertigo; OT12  
 Benign Prostatic Hyperplasia; FM17, U8  
 Bennett's Fracture; PL26  
 Benzodiazepines; A25, PS48  
 Bereavement; PS18  
 Berlin Criteria; R26  
 Bethesda Criteria; GS34  
 Bias; PH8  
 Biliary Atresia; P75  
 Biliary Cirrhosis; G42  
 Biliary Colic; GS46  
 Biliary Tract; G3  
 Bilirubin; G28, G41, GS6  
 Biophysical Profile; OB12  
 Biopsy  
   Genital Tract; GY9  
   Skin; PL7  
 Bipolar Disorders; PS12  
   Pediatric; PS34  
 BI-RADS; MI31  
 Bishop Score; OB36  
 Bites; ER46  
 Bladder Carcinoma; U22  
 Bladder Catheterization; U41  
 Bladder Hemorrhage; U4  
 Bladder Pain Syndrome; U13  
 Bladder Trauma; U33  
 Blastomycosis; ID28  
 Blasts; H4  
 Bleeding, Abnormal; P50  
 Bleeding Disorders; P49  
   Neonatal; P70  
 Bleeding in Pregnancy; OB22  
 Bleeding Peptic Ulcers; G13  
 Bleeding, Uterine; GY6, GY14  
 Bleed, Vaginal; ER39  
 Blepharitis; OP14  
 Blind-Loop Syndrome; GS21  
 Blood Film Interpretation; H3  
 Blood Groups; H50  
 Blood, Intracranial; NS16  
 Blood Pressure; A12  
   Regulation; NP2  
 Blood Products; A15, H50  
 Blood Transfusions; H50  
   Reactions; H52  
 Blow-Out Fracture; OP43, PL31  
 Boas' Sign; GS46  
 BODE Index; R10  
 Body Dysmorphic Disorder; PS26  
 Body Mass Index; FM7  
 Boerhaave's Syndrome; GS14  
 Boils; D26  
 Bone Abscess; MI24  
 Bone Imaging; MI28  
 Bone Metastases; OR45  
 Bone Scintigraphy; MI22  
 Bone Tumour; MI23, OR42  
 Borderline Personality Disorder; PS32  
 Bosniak Classification; U19  
 Botulism; N32, N34  
 Bouchard's Nodes; RH5  
 Boutonniere Deformity; PL24  
 Bouveret's Syndrome; GS48  
 Bowel; G3  
   Obstruction; GS24, MI12, MI13  
 Bowen's Disease; D35

Bowman's Space/Capsule; NP2  
 Boxer's Fracture; PL26  
 Boznik Classification; MI16  
 Brachial Plexus Anatomy; PL4  
 Brachial Plexus Injuries; PL28  
 Bradyarrhythmias; C14, ER31  
 Bradycardia Algorithm; A29  
 Bradycardia, Intraoperative; A12  
 Bradykinesia; N26  
 Brain  
   Imaging; MI26  
   Injury; ER8, N22, NS31  
   Lesions; NS4  
   Metastasis; NS11  
   Brain Tumours; NS10  
     Pediatric; NS38  
 Brainstem; N4  
 Branchial Cleft Cysts/Fistula; OT32  
 Branch Retinal Artery Occlusion; OP24  
 Breaking Bad News; ELOAM11  
 Breast  
   Abscess; GS55  
   Cancer Screening Guidelines; FM3  
   Imaging; MI30  
   Mass; GS54, MI32  
   Reconstruction; PL32  
   Reduction; PL33  
   Tissue Expanders; PL33  
 Breastfeeding; OB53, P6  
   Problems; OB52  
 Breath Holding Spells; P8  
 Breathing; ER3  
 Breech Fetal Presentation; OB40  
 Brian's Law; PS51  
 Broca's Area; N21  
 Bronchiectasis; R11  
 Bronchiolitis, Pediatric; P93  
 Bronchitis; FM18  
   Chronic; R8  
 Bronchogenic Cancer; R28  
 Bronchopulmonary Dysplasia; P71  
 Bronchoscopy; R4  
 Brown-Séquard Syndrome; NS29  
 Bruce Protocol; C10  
 Brudzinski's Sign; ID19  
 Bruise; ER18  
 Bruising, Abnormal; P50  
 B-Symptoms; H11  
 Bulimia Nervosa; PS30  
 Bullous Pemphigoid; D20  
 Bunions; OR37  
 Burkitt's Lymphoma; H44  
 Burns; ER45, PL16  
   Chemical; PL21  
   Depth; PL18  
   Electrical; PL21  
   Healing; PL19  
   Management; PL18  
 Buspirone; PS49

## C

Calcaneal Fracture; OR36  
 Calcineurin Inhibitor Nephropathy; NP19  
 Calcium; FM44  
 Calcium Homeostasis; E38  
 Callus; D7  
 Caloric Reflexes; N2  
 Campbell De Morgan Spot; D10  
 Campbell Telangiectasia; D10  
 Canada Health Act; ELOAM17  
 Canada's Food Guide; FM5  
 Canadian Cholesterol Guidelines; FM9

Canadian C-spine Rule; ER10, OR22  
 Canadian CT Head Rule; ER8  
 Canadian Diabetes Guidelines; E8  
 Cancer  
   Anal; GS41  
   Bladder; U22  
   Breast; GS55, MI30  
   Bronchogenic; R28  
   Cervix; GY42  
   Colon; GS33  
   Colorectal; GS34  
   Endometrial; GY36  
   Esophagus; GS14  
   Fallopian Tube; GY48  
   Gallbladder; GS49  
   Gastric; GS18  
   Head and Neck; OT34  
   Liver; GS43  
   Lung; R27  
   Ocular; OP34  
   Ovary; GY38  
   Pancreas; GS51  
   Pediatric; P50  
   Penile; U27  
   Prostate; U23  
     Screening; U25  
   Renal Pelvis; U21  
   Renal Wall; U20  
   Skin; D33  
   Testicular; U26  
   Thyroid; OT37  
   Ureter; U21  
   Uterus; GY36  
   Vagina; GY47  
   Vulva; GY45  
*Candida albicans*; ID30  
 Candidal Endophthalmitis; OP35  
 Candidiasis; D31, GY25  
 Cannabis Dependence/Abuse; PS25  
 Capacity; ELOAM5, ELOAM6  
 Capillary Hemangioma; D10, P78  
 Carbapenems; ID47  
 Carbon Monoxide Poisoning; ER46, PL19  
 Carbuncle; D26  
 Cardiac  
   Anatomy; C3  
   Arrest; A11, C28  
     Algorithm; A28  
   Biomarkers; C9  
   Dysrhythmias; ER31  
   Imaging; MI27  
   Silhouette, Enlarged; MI9  
   Tamponade; C43, ER12  
   Transplantation; C34  
 Cardiomyopathy; C35, C36  
 Caregiver Abuse Screen (CASE); GM5  
 Caries; P9  
 Carney's Triad; GS19  
 Carotid Stenosis; NS23  
 Carpal Tunnel Syndrome; N31, PL27  
 Case-Control Study; PH12  
 Casts; NP6  
 Cataracts; OP21  
 Catecholamine; E36  
 Catheter Ablation; C21  
 Catheterization, Cardiac; C11  
 Cat Scratch Disease; ID27  
 Cauda Equina Syndrome; NS26  
 Causation; PH16  
 Cavemous Malformations; NS24  
 Cavemous Sinus; N9  
 Celiac Disease; G18, P37  
 Cellulitis; D25, ID10, PL14  
 Cell Wall Inhibitors; ID48  
 Central/Branch Retinal Vein Occlusion; OP24

Central Corneal Thickness; OP8  
 Central Pontine Myelinolysis; NP8  
 Central Retinal Artery Occlusion; OP23  
 Central Retinal Vein Occlusion; N11  
 Central Venous Access; MI29  
 Central Venous Catheter; MI10  
 Cephalosporins; ID46  
 Cerebellar Ataxias; N29  
 Cerebellar Disorders; N28  
 Cerebral Abscess; MI22, NS15  
 Cerebral Angiography; MI19  
 Cerebral Blood Flow; NS5  
 Cerebral Hemorrhage; N46  
 Cerebral Palsy; P90  
 Cerebritis; MI22  
 Cerebrovascular Disease; MI20, NS18  
 Certain Safety Factor; CP9  
 Cerumen Impaction; OT15  
 Cervical Cancer; GY42  
   Screening; FM4  
 Cervical Disc Syndrome; NS24  
 Cervical Lesions; GY42  
 Cervical Radiculopathy/Neuropathy; OR22  
 Cervical Ripening; OB37  
 Cervical Spine; OR21  
   Fractures; NS34  
 Cervical Stenosis/Spondylosis; NS25  
 Cervix; OB31  
 Cesarean Delivery; OB47  
 Cestodes; ID35  
 CHA2DS2-VASc Score; C16  
 CHADS2 Risk Prediction Score; C17  
 Chadwick's Sign; OB2  
 Chagas Disease; ID33  
 Chalazion; OP14  
 Charcot's Triad; G43, GS48  
 Charge Syndrome; P44  
 Chemical Burns; PL21  
 Chemical Ocular Burns; ER42, OP43  
 Chemotherapeutic Agents; H56  
 Chemotherapeutic Regimens; H43  
 Cherry Angioma; D10  
 Chest Pain; C4, ER21, FM18, R3  
   Treatment Algorithm; C27  
 Chest Tube; MI10  
 Chest X-Ray; MI4, R4  
 Chiari Malformations; NS37  
 Chicken Pox; D40  
 Child Abuse; ER59  
 Childhood Disintegrative Disorder; PS37  
 Child Psychiatry; PS33  
 Child-Pugh Score; G37  
 Child-Turcotte-Pugh Score; GS44  
 Chi-square Test; PH15  
 Chlamydia; GY26  
 Cholangiocarcinoma; GS49  
 Cholangitis, Acute; GS48  
 Cholangitis, Ascending; G43  
 Cholangitis, Sclerosing; G41  
 Cholecystitis; MI15  
 Cholecystitis, Acalculous; GS47  
 Cholecystitis, Acute; GS46  
 Cholecystostomy; MI30  
 Choledochal Cysts; GS42  
 Choledocholithiasis; GS47  
 Cholelithiasis; GS45  
 Cholestatic Jaundice of Pregnancy; OB19  
 Cholesteatoma; OT17  
 Cholesterol; FM8  
 Cholesterol Stones; GS45  
 Chondral Defects; OR10  
 Chondrocalcinosis; MI25  
 Chondromalacia Patellae; OR33  
 Chondrosarcoma; OR44  
 Chorea; N25

- Chorioamnionitis; OB46  
 Choriocarcinoma; GY49  
 Chorionic Villus Sampling; OB7  
 Christmas Disease; H29  
 Chronic Cerebrospinal Venous Insufficiency; N46  
 Chronic Disease Anemia; H15, P48  
 Chronic Fatigue Syndrome; FM33  
 Chronic Inflammatory Demyelinating Polyneuropathy; N31  
 Chronic Kidney Disease; NP34  
 Chronic Lung Disease; P71  
 Chronic Lymphocytic Leukemia; H46  
 Chronic Myeloid Leukemia; H38  
 Chronic Obstructive Pulmonary Disease; ER32, FM16, GS17, R8  
 Chronic Pelvic Pain Syndrome; U15  
 Chronic Venous Insufficiency; C51  
 Churg-Strauss Syndrome; R20  
 Churg-Strauss Triad; RH17  
 Chvostek's Sign; E40  
 Cine Esophagogram; MI13  
 Circadian Rhythm; N42  
 Circle of Willis, Aneurysms of; NS3  
 Circulation; ER3  
 Circulation, Coronary; C2  
 Circumcision; P8, U40  
 Cirrhosis; G34, G36  
     Biliary; G42  
 Citrate Toxicity; H53  
 CIWA-A Scale; PS23  
 Claudication; C45, OR23  
 Clavicle Fracture; OR14  
 Clearance; CP7  
 Cleft Lip/Palate; PL34  
 Climate Change; PH21  
 Clinical Significance; PH14  
 Clinical Testing; CP2  
*Clonorchis sinensis*; ID35  
 Closed Reduction; OR6  
*Clostridium difficile*; ID7  
 Clotting Factors; H25  
 Clubbing; R3  
 Club Drugs Dependence/Abuse; PS25  
 Club Foot; OR41  
 Cluster Headache; N39  
 CN III Palsy; OP31  
 CNS Infection; NS15  
 CNS Tumours; NS10  
 Coagulation Factors; H52  
 Coal Worker's Pneumoconiosis; R15  
 Coarctation of the Aorta; P18  
 Cobalamin; H22  
 Cobb Angle; OR42  
 Cocaine Dependence/Abuse; PS24  
 Coccidioidomycosis; ID28  
 Cockcroft-Gault Equation; CP6, NP4  
 Cognitive Assessment; PS3  
 Cognitive Behavioural Therapy; PS41  
 Cognitive Disorders; PS19  
 Cognitive Therapy; PS40  
 Cohort Study; PH12  
 Cold, Common; FM19  
 Cold Injury; ER44  
 Colic, Biliary; GS46  
 Colic, Infantile; P11  
 Collateral Ligament Stress Test; OR30  
 Collateral Ligament Tears; OR31  
 Colles' Fracture; OR19  
 Colloid Infusion; A14  
 Colonic Pseudo-Obstruction; GS26  
 Colonography; MI13  
 Colonoscopy; MI13  
 Colorectal Cancer Screening Guidelines; FM4  
 Colorectal Carcinoma; GS34  
 Colorectal Polyps; GS33  
 Colostomy; GS37  
 Colour Vision Test; OP6  
 Colposcopy; GY9  
 Coma; ER20, NS34  
 Community Treatment Order; PS51  
 Compartment Syndrome; ER16, OR8, PL23  
 Complete Blood Count; H3  
 Complete Heart Block; P21  
 Complex Regional Pain Syndrome; N38, OR6  
 Compliance; PH10  
 Computed Tomography; MI2  
     Chest; MI6  
 Concussion; N22, NS31  
 Conduct Disorder; PS38  
 Conduction Abnormalities; C6  
 Condyloma Acuminata; D30  
 Confidence Interval; PH15  
 Confidentiality; ELOAM8  
 Confounder; PH8  
 Confusion, Acute; N17  
 Confusion and Agitation, Post-Operative; A17  
 Congenital Adrenal Hyperplasia; P31  
 Congenital Diaphragmatic Hernias; GS61  
 Congenital Glaucoma; OP42  
 Congenital Hand Anomalies; PL34  
 Congenital Heart Disease; P16  
     Acyanotic; P17  
     Cyanotic; P19  
 Congenital Hyperthyroidism; P29  
 Congenital Hypothyroidism; P30  
 Congenital Sensorineural Hearing Loss; OT18  
 Congenital Talipes Equinovarus; OR41  
 Congenital Urological Abnormalities; U36  
 Congestive Heart Failure; C30, ER33  
     Pediatric; P20  
 Conjunctiva; OP14  
 Conjunctivitis; OP5, OP15  
 Connective Tissue Disease; RH16  
 Consent; ELOAM5, ER6  
     Exceptions; ELOAM6  
 Consolidation; MI6  
 Constipation; G5, G24, GM3  
     Pediatric; P38  
 Constricted Pupil; OP32  
 Continuous Quality Improvement (CQI); PH17  
 Contraception; FM20, GY19  
     Emergency; FM21  
 Contrast Echocardiography; C10  
 Contrast Enhancement; MI3  
 Contrast Studies; MI13  
 Contusion; ER17  
 Conus Medullaris Syndrome; NS26  
 Conversion Disorder; N15, PS26  
 Convulsions; N15  
 Coordination Exam; N4  
 Corn; D7  
 Cornea; OP17  
 Corneal Abrasion; OP5, OP17  
 Corneal Ulcer; OP5, OP18  
 Coronary Artery Bypass Graft Surgery; C29  
 Coronary Artery Disease; E4  
 Coronary Revascularization; C28  
 Coroner; ELOAM13  
 Cortisol; E30  
 Cost Analysis; PH18  
 Cough; FM21, R3  
 Courvoisier's Gallbladder; GS49  
 Courvoisier's Sign; GS49  
 Coxa Plana; OR40  
 CPR Guidelines; ER5  
 Cranial Nerve Deficits; N8  
 Cranial Nerve Injury; NS31  
 Cranial Nerves Exam; N2  
 Craniofacial Anomalies, Pediatric; PL34  
 Craniofacial Buttresses; PL5  
 Craniofacial Injuries; PL28  
 Craniosynostosis; NS38, PL34  
 Creatinine; NP4  
 Crescentic Glomerulonephritis; NP22  
 CREST Syndrome; RH13  
 Creutzfeldt-Jakob Disease; N21  
 Crigler-Najjar Syndrome; G41  
 Crohn's Disease; G19, G20, GS30  
 Cross-Sectional Study; PH12  
 Croup; ER57, OT44, P92  
 Cruciate Ligament Tears; OR30  
 Crude Death Rate; PH7  
 Crying/Fussing Child; P8  
 Cryoglobulinemia; NP24  
*Cryptococcus spp.*; ID30  
 Cryptogenic Fibrosing Alveolitis; R13  
 Cryptorchidism; GS63, U39  
*Cryptosporidium spp.*; ID32  
 Crystal-Induced Arthropathies; RH24  
 Crystalloid Infusion; A14  
 Crystals; NP7  
 C-Section; OB47  
 C-Spine; OR21  
 Cullen's Sign; G45  
 CURB 65 Score; ID9  
 Cushing's Syndrome; E33  
 Cutaneous Glands; D2  
 Cutaneous T-Cell Lymphoma; D36  
 Cutaneous Vasculitis; RH18  
 Cutis Marmorata; P78  
 Cyanide Poisoning; ER46  
 Cyanosis, Neonatal; P71  
 Cyclothymia; PS13  
 Cyst; D5  
 Cystadenocarcinoma; GS42  
 Cystadenoma; GS42  
 Cystatin C; NP5  
 Cystic Echinococcosis; GS42  
 Cystic Fibrosis; P95, R11  
 Cystic Kidney Disease; U19  
 Cystitis; U12  
     Interstitial; U13  
     Recurrent/Chronic; U13  
 Cystocele; GY35  
 Cystoscopy; U41  
 Cytochrome P450 System; CP5

## D

- Dacryoadenitis; OP12  
 Dacryocystitis; OP12  
 Dandy-Walker Malformation; NS37  
 Danis-Weber Classification; OR35  
 Data Analysis; PH14  
 Dawson's Fingers; MI21  
 Death; ELOAM13  
 Death, Neurologically Determined; NS34  
 Death Rattle; GM13  
 Decontamination; ER51  
 Deep Brain Stimulation; PS50  
 Deep Neck Space Infection; OT46  
 Deep Venous Thrombosis; ER33  
 Defense Mechanisms; PS39  
 Degenerative Arthritis; RH5  
 Degenerative Disc Disease; OR23  
 Dehydration; A14  
     Infant/Child; P79  
 Delayed Puberty; P33  
 Delirium; GM3, N17, PS19  
 Delirium Tremens; PS22  
 Delivery; OB31  
 Delusional Disorder; PS8  
 Delusions; PS3

Dementia; FM21, GM3, N17, PS20  
 Dementia, Frontotemporal; N20  
 Dementia with Lewy Bodies; N20  
 Dengue; ID38  
 Denis Classification; NS33  
 Dentition; P9  
 Denys-Drash Syndrome; P52  
 Dependent Personality Disorder; PS32  
 Depressed Newborn; P68  
 Depression; FM21, GM3, PS9  
     Postpartum; OB51  
 Depressive Disorders; PS10  
 De Quervain's Tenosynovitis; PL24  
 Dermal Melanocytosis; D8  
 Dermatitis; D13, FM45  
     Atopic; D14  
     Contact; D15  
     Herpetiformis; D21  
     Pediatric; P12  
     Perioral; D12  
 Dermatofibroma; D6  
 Dermatomyositis; RH8, RH15  
 Dermatophytoses; D26  
 Dermatoses, Life Threatening; ER42  
 Dermis; D2  
 Determinants of Health; PH3  
 Developmental Concepts; PS33  
 Developmental Delay; P22  
 Developmental Disorders; PS36  
 Developmental Milestones; P5  
 DEXA; MI24  
 Dextrose; ER50  
 Diabetes Insipidus; E19, NP11  
 Diabetes Mellitus; E6, FM22, NP28  
     Medications; E52  
     during Pregnancy; OB13  
     Pediatric; P26  
 Diabetic Foot Infections; ID16  
 Diabetic Ketoacidosis; ER35, E11  
 Diabetic Neuropathy; N31, N37  
 Diabetic Retinopathy; OP35  
 Diabetic Ulcers; PL15  
 Dialectical Behavioural Therapy; PS41  
 Dialysis; NP36  
 Diaphragmatic Hernia; P72  
 Diarrhea; FM26, G5, G15  
     Acute; G15, ID11  
     Chronic; G16  
     Infectious; ID13, P36  
     Pediatric; P35  
     Postvagotomy; GS21  
     Toddler's; P37  
     Traveller's; ID14  
 Dietary Requirement; P6  
 Diethylstilbestrol Syndrome; GY47  
 Diffuse Esophageal Spasm; G9  
 Diffuse Large B-Cell Lymphoma; H44  
 Diffusion Weighted Imaging; MI3  
 DiGeorge Syndrome; P44  
 Digitalis; C8  
 Digital Rectal Exam; U25  
 Dilatation and Curettage; GY10  
 Dilated Cardiomyopathy; C36  
 Dilated Pupil; OP32  
 Diphtheria; P56  
*Diphyllobothrium latum*; ID35  
 Diplopia; N13, OP4, OP7  
 Disability Adjusted Life Year; PH7  
 Disc Disease; OR23  
 Disc Herniation; OR24  
 Discontinuation Syndrome; PS47  
 Disease Modifying Anti-Rheumatic Drugs; RH10  
 Disease Prevention; PH4  
 Dislocated Lens; OP21  
 Dislocation; MI23

Disseminated Intravascular Coagulation; H30  
 Dissociative Disorders; PS27  
 Distal Femoral Fracture; OR29  
 Distributions Analysis; PH14  
 Diuretics; NP3  
 Diverticulitis; GS31, MI15  
 Diverticulosis; GS31  
 Dix-Hallpike Maneuver; FM27, OT13  
 Dizziness; FM26, OT5, OT12  
 Doctor-Patient Relationship; ELOAM4  
 Döhle Bodies; H8  
 Domestic Violence; ER29, FM28  
 Double Vision; OP4  
 Down Syndrome; P43  
 Drains; GS8  
 Drawer Tests; OR29  
 Driving Competency; GM10  
 Drop Attacks; OT13  
 Drowning, Near; ER47  
 Drug  
     Absorption; CP3  
     Administration; CP2  
     Biotransformation; CP5  
     Distribution; CP4  
     Effectiveness and Safety; CP9  
     Efficacy; CP7  
     Elimination; CP6  
     Endings; CP14  
     Eruptions; D22  
     Hypersensitivity Syndrome; D22  
     Interactions; CP12  
     Metabolism; CP5  
     Nomenclature; CP2  
     Otototoxicity; OT20  
     Potency; CP7  
     Response; CP11  
 Dry Eye Syndrome; OP11  
 Dubowitz/Ballard Scores; P66  
 Duchenne-Erb Palsy; PL28  
 Duchenne Muscular Dystrophy; P44  
 Ductal Hyperplasia; GS55  
 Duke Criteria; ID17  
 Duke Treadmill Score; C10  
 Dumping Syndrome; GS21  
 Duodenal Ulcers; GS17  
 Duodenum; G2  
 Dupuytren's Disease; PL26  
 Duty to Protect/Warn; ELOAM9  
 Duty to Report; ER6  
 Dysfunctional Uterine Bleeding; GY15  
 Dyslipidemia; E2, FM8  
     Medications; E53  
 Dysmenorrhea; GY6, GY15  
 Dysmorphic Child; P41  
 Dyspareunia; GY8, GY32  
 Dyspepsia; FM29, G5, G10  
 Dysphagia; G4, G8  
 Dysplasia of the Hip; OR40  
 Dyspnea; C5, ER27, FM29, R3  
     Pediatric; P92  
     Postoperative; GS10  
 Dysrhythmias; ER31  
     Pediatric; P21  
 Dysthymia; PS11  
 Dystocia; OB43  
 Dystonia; N25, N27  
 Dystonia Neurosurgery; NS39  
 Dystrophy; N35  
 Dysuria; FM30, U5

## E

Ear Anatomy; OT2  
 Early Developmental Impairment; P22  
 Ear Wax; OT15  
 Eating Disorders; PS29  
 Ebstein's Anomaly; P19  
 ECG, Ambulatory; C9  
 Echinocandins; ID53  
*Echinococcus granulosus*; ID35  
 Echocardiography; C9  
 Eclampsia; OB17  
 Ecological Study; PH12  
 Ecstasy; PS25  
 Ectopia Lentis; OP21  
 Ectopic Pregnancy; OB23  
 Ectopic Testes; U39  
 Ectropion; OP13  
 Eczema; D13  
 Edema; C4  
 Edmonton Symptom Assessment System; GM12  
 Edwards Syndrome; P43  
 Effectiveness; PH11  
 Efficacy; PH11  
 Efficiency; PH11  
 Elbow Dislocation; OR17  
 Elder Abuse; FM28, GM4  
 Electrical Burns; PL21  
 Electrical Pacing; C21  
 Electrocardiography (ECG); C5  
 Electroconvulsive Therapy; PS49  
 Electrolyte Balance; NP2  
 Electrolyte Disorders; NP7  
 Electrolyte Disturbances; C8, ER36  
     Pediatric; P80  
 Electrophysiology Studies; C21  
 Elimination Kinetics; CP7  
 Eosinophilia; H10  
 Eosinophilic Esophagitis; G8  
 Eosinophilic Esophagitis; G8  
 Ephelides; D8  
 Epicondylitis; OR18



Epidemiology; PH7  
 Epidermis; D2  
 Epididymitis; U15  
 Epidural Anesthesia; A20  
 Epidural Hematoma; MI18, NS17  
 Epiglottitis; ER57, P92  
   Acute; OT45  
 Epilepsy; N14, P86  
 Epilepsy Neurosurgery; NS40  
 Epiphora; OP12  
 Epiphyseal Injury; OR39  
 Episcleritis; OP16  
 Episiotomy; OB47  
 Epispadias-Exstrophy Complex; U38  
 Epistaxis; ER23, FM31, OT26  
 Erectile Dysfunction; FM31, U30  
 Eruptions, Exanthematous; D23  
 Erysipelas; D25, PL14  
 Erythema Infectiosum; D40, P58  
 Erythema Multiforme; D22, ER42  
 Erythema Nodosum; D42  
 Erythema Toxicum; P78  
 Erythrocyte; H3  
 Erythrocytosis; H6  
*Escherichia coli*; ID7  
 Esophageal Diverticula; G9  
 Esophageal Injury; ER12  
 Esophageal Perforation; GS14  
 Esophageal Varices; G26  
 Esophagitis, Eosinophilic; G8  
 Esophagitis, Infectious; G10  
 Esophagus; G2  
 Esotropia; OP40  
 Essential Thrombocythemia; H40  
 Estrogen; GY4  
 Ethics; ELOAM3  
 Euthanasia; ELOAM13  
 Evidence Assessment; PH16  
 Ewart's Sign; C42  
 Ewing's Sarcoma; OR44  
 Exercise; FM10  
 Exercise Testing; C10  
 Exophthalmos; OP10  
 Exostoses; OT15  
 Experimental Study Designs; PH13  
 External Ear Diseases; OT15  
 Extracorporeal Shock Wave Lithotripsy; U43  
 Extradural Hematoma; NS17  
 Extraocular Muscles Test; OP6  
 Extrapyrmidal Symptoms; PS44  
 Extrinsic Allergic Alveolitis; R14  
 Extubation; A17  
 Eye Anatomy; OP2  
 Eye Erosions; OP18  
 Eye Floaters; OP4, OP22  
 Eye Fractures; PL31  
 Eye Movements, Abnormalities of; N12

## F

Facial Bones; PL4  
 Facial Injuries; PL29  
 Facial Nerve; N10  
 Facial Nerve Paralysis; OT21  
 Factor VIII; H34  
 Factor V Leiden; H34  
 Factor XI Deficiency; H29  
 Failure to Thrive, Elderly; GM6  
 Failure to Thrive, Pediatric; P10  
 Fallopian Tube; GY3  
 Fallopian Tube Cancer; GY48  
 Falls; ER7  
   Elderly; GM5

Familial Adenomatous Polyposis; GS33  
 Familial Medullary Thyroid Cancer; E37  
 Fanconi Syndrome; NP25  
 Fasting Guidelines; A3  
 Fatigue; FM32  
 Fat Necrosis; GS55  
 Fatty Liver Disease; G34, G35  
 Febrile Infant; ER58  
 Febrile Neutropenia; ID39  
 Febrile Seizures; ER58, P87  
 Fecal Incontinence; GM7  
   Pediatric; P9  
 Feeding Difficulty; OT44  
 Femoral Diaphysis Fracture; OR28  
 Ferritin; H13  
 Fetal Alcohol Spectrum Disorder; P24  
 Fetal Heart Rate; GB34  
 Fetal Monitoring in Labour; OB34  
 Fetal Oxygenation; OB35  
 Fetal Scalp Blood Sampling; OB34  
 Fetal Tissue; ELOAM14  
 Fetus during Delivery; OB31  
 Fever; FM34  
   Returned Traveller; ID37  
   Unknown Origin; ID38  
   Pediatric; ER58, P54  
   Postoperative; GS7  
   Postpartum; OB50  
 Fibrinolysis, Disorders of; H34  
 Fibroadenoma; GS54  
 Fibroids; GY17  
 Fibromyalgia; RH27  
 Fibrosis, Pulmonary; R13  
 Fibrous Cortical Defect; OR43  
 Fifth Disease; P58  
 Filtration Fraction; NP4  
 Finger Amputation; PL24  
 First Trimester Screen; OB6  
 Fisher Grade; NS18  
 Fistula; GS37  
 Fistula-In-Ano; GS39  
 Fistulotomy; GS40  
 Fitzpatrick Skin Phototypes; D3  
 Flail Chest; ER12  
 Flaps; PL12  
 Flatulence; G4  
 Flatworms; ID35  
 Flexor Tendon Deformities; PL25  
 Fluid Balance; A13  
 Fluid Resuscitation; ER4  
 Flukes; ID36  
 Flunitrazepam; PS25  
 Fluoroquinolones; ID47  
 Fluoroscopy; MI2  
 Focal Nodular Hyperplasia; GS43  
 Folate Deficiency Anemia; H23, OB13  
 Folic Acid Supplementation; FM3  
 Folie à Deux; PS8  
 Follicle Stimulating Hormone; E18  
 Follicular Lymphoma; H44  
 Folliculitis; D26  
 Food Contaminants; PH22  
 Foot Fracture; OR36  
 Forceps; OB46  
 Forearm Fracture; OR18  
 Foreign Body Ingestion/Inhalation; OT46  
 Foreign Body in the Eye; OP17  
 Forrest Classification; G26  
 Fractional Excretion of Sodium; NP7

Fracture; ER16, MI22  
   Ankle; OR35  
   Basal Skull; PL29  
   Clavicle; OR14  
   Elbow; OR16  
   Femur; OR28  
   Foot; OR36  
   Forearm; OR18  
   General Principles; OR5  
   Hip; OR26  
   Humerus; OR15  
   Mandibular; PL29  
   Maxillary; PL30  
   Naso-orbital Ethmoid; PL31  
   Nose; PL30  
   Open; OR8  
   Orbital Floor; PL31  
   Patella; OR32  
   Pediatric; OR38  
   Pelvis; OR25  
   Scaphoid; OR20  
   Spine; OR21  
   Stress; OR39  
   Temporal Bone; OT21  
   Tibia; OR34  
   Wrist; OR19  
   Zygomatic; PL31  
 Fragile X Syndrome; P43  
 Frailty (Elderly); GM6  
 Framingham Risk Score; E5, FM8  
 Freckles; D8  
 Free ABD0; MI11  
 Friedrich's Ataxia; N29  
 Frontotemporal Dementia; N20  
 Frostbite; ER45  
 Fugue; PS27  
 Functional Endoscopic Sinus Surgery; OT25  
 Fundoscopy; OP8  
 Fungal Infection; ID28  
 Furuncle; D26

## G

G6PD Deficiency; H22  
 GABHS; FM50  
 Gadolinium-Chelates; MI3  
 Gaisböck's Syndrome; H6  
 Gait Disturbances; N29  
 Galactosemia; P46  
 Galeazzi Fracture; OR19  
 Galeazzi's Sign; OR40  
 Gallstone Disease; G44, GS45  
 Gallstone Ileus; GS48  
 Gallstone Pancreatitis; GS50  
 Gamma Hydroxybutyrate; PS25  
 Ganglion Cyst; PL24  
 Garden Classification; OR27  
 Gardner's Syndrome; GS34  
 Gastric Acid Secretion; G11  
 Gastric Carcinoma; GS18  
 Gastric Ulcers; GS17  
 Gastrinoma; GS60  
 Gastritis; G11  
 Gastroenteritis; P56  
 Gastroesophageal Reflux Disease; G6  
 Gastroesophageal Reflux, Pediatric; P35  
 Gastrointestinal Bleed; G5, GS5  
   Lower; G27, P40  
   Upper; G25  
 Gastrointestinal Stromal Tumour; GS19  
 Gastrointestinal Tract Anatomy; G2  
 Gastrojejunostomy; MI30  
 Gastroschisis; GS62



Gastrostomy; M130  
 Gaze, Disorders of; N12  
 Gender Dysphoria; PS28  
 Generalized Anxiety Disorder; PS15  
   Pediatric; PS35  
 Genetic Anomalies; P41  
 Genetics; P42  
 Genetic Syndromes; P43  
 Genetic Testing, Prenatal/Antenatal; ELOAM15  
 Genitalia, Ambiguous; P30  
 Genital Ulcers; GY28  
 Genital Warts; GY27  
 Genitourinary System Imaging; M127  
 Genito-Urinary Tract Anatomy; U2  
 Geriatric Giants; GM2  
 Gerstmann's Syndrome; N22  
 Gestational Age and Size; P66  
 Gestational Diabetes Mellitus; OB14  
 Gestational Hypertension; OB15  
 Gestational Trophoblastic Disease; GY48  
 Gestational Trophoblastic Neoplasia; GY48  
 Gestation, Multiple; OB28  
 GHB; PS25  
 Gianotti-Crosti Syndrome; D41, P58  
 Giant Cell Arteritis; OP38, RH20  
 Giant Cell Tumours; OR43  
*Giardia lamblia*; ID32  
 Gilbert's Syndrome; G41  
 Gilles de la Tourette's Syndrome; N28  
 Glasgow Coma Scale; ER4, NS30  
   Modified; ER56  
 Glaucoma; ER42, OP27  
   Congenital; OP42  
 Global Assessment of Functioning; PS4  
 Global Developmental Delay; P22  
 Globe Displacement; OP10  
 Glomerular Disease; NP19  
 Glomerular Filtration Rate; NP4  
 Glomerulonephritis; NP22  
   Post-Streptococcal; P62  
 Glomerulosclerosis; NP23, NP29  
 Glomerulus; NP2  
 Glossopharyngeal Nerve; N10  
 Glucocorticoid; E30  
 Glucose; ER50  
 Glucose, Fasting; E6  
 Glucose Homeostasis; NP2  
 Gluten Enteropathy; G18  
 Glycemic Targets; E8  
 Goitre, Non-Toxic; E28  
 Golfer's Elbow; OR18  
 Gonioscopy; OP6  
 Gonococcal Arthritis; ID15  
 Gonococcal Infection; ER43  
 Gonococcemia; D32  
 Gonorrhea; GY27  
 Goodell's Sign; OB2  
 Goodpasture's Disease; NP24, R20  
 Goodsall's Rule; GS40  
 Gottron's Papules/Sign; RH15  
 Gout; RH24, RH25  
 Gower's Sign; P44  
 Grafts; PL11  
 Graft Versus Host Disease; H53  
 Granulomatosis with Polyangiitis; NP24, R20, RH18  
 Graves' Disease; E23  
   Neonatal; P29  
   Ophthalmopathy; OP37  
 Greenstick Fracture; OR38  
 Grey-Turner's Sign; G45  
 Group A  $\beta$ -hemolytic Streptococcus; FM50  
 Group B Streptococcus Screen; OB8  
 Growing Pains; P97  
 Growth; P4, P27  
 Growth Hormone; E17

Growth Hormone Deficiency; P28  
 Guillain-Barré Syndrome; N32  
 Gunshot Wound; ER7  
 Gustilo Classification; OR8  
 Gynecological Imaging; M117  
 Gynecological Infections; GY24  
 Gynecomastia; E49

**H**

HAART; ID44  
 Hair Follicle Infections; D26  
 Hair Loss; D37  
 Half-Life; CP6  
 Hallucinogens Dependence/Abuse; PS25  
 Hallux Valgus; OR37  
 Hampton's Hump; R18  
 Hand  
   Amputation; PL24  
   Anatomy; PL2  
   Anomalies, Congenital; PL34  
   Dislocations; PL25  
   Fractures; PL25  
   Infections; PL23  
   Rheumatoid; PL27  
   Tendon Deformities; PL24  
   Trauma; PL22  
 Hand, Foot and Mouth Disease; D41, P58  
 Hansen's Disease; ID24  
 Hartmann Procedure; GS32  
 Hashimoto's Thyroiditis; E27  
 Hawkins-Kennedy Test; OR13  
 Hay Fever; OT23  
 HbA1c; E8  
 Headache; ER24, FM36, N38  
   Pediatric; P88  
 Head and Face Anatomy; OT4  
 Head and Neck Neoplasms; OT34  
 Head Injury; ER8, NS31  
 Health and Disease Measurements; PH7  
 Health Care Institutions; GM11  
 Health Care Services; GM11  
 Health Concepts; PH3  
 Health Determinants; PH3  
 Health Promotion Strategies; PH5  
 Health Services Cost Analysis; PH18  
 Health Services Quality; PH17  
 Hearing Aids; OT12  
 Hearing Impairment; FM37  
 Hearing Loss; OT6, OT9  
   Congenital; OT18  
   Noise-Induced; OT20  
   Sudden; OT19  
 Hearing Physiology; OT9  
 Heartburn; G6  
 Heart Chamber Enlargement; C7  
 Heart Failure; C30  
 Heart Hypertrophy; C7  
 Heart Murmurs; P21  
 Heart Rate; A11  
 Heat Exhaustion; ER43  
 Heat Stroke; ER44  
 Heavy Metal Toxicity; PH23  
 Heberden's Nodes; RH5  
 Heel Spur Syndrome; OR37  
 Heerfordt-Waldenström Syndrome; R14  
 Hegar's Sign; OB2  
 HELLP Syndrome; OB17, OB19  
 Helminths; ID5, ID34  
 Hemangioma; D10  
 Hematocele; U29  
 Hematochezia; G26

Hematologic Malignancies; H35  
   Complications; H49  
 Hematoma Blocks; A22  
 Hematopoiesis; H2  
 Hematuria; NP21  
   Macroscopic (Gross); U4  
   Microscopic; U5  
 Hemianopsia; N12  
 Hemiptera; D28  
 Hemochromatosis; G33  
 Hemodialysis; NP36  
 Hemolytic Anemia; H17  
 Hemolytic Uremic Syndrome; H28, P81  
 Hemophilia; H29  
 Hemoptysis; R3  
 Hemorrhage, Antepartum; OB25  
 Hemorrhage, Neonatal; P73  
 Hemorrhage, Postpartum; OB48  
 Hemorrhage, Subconjunctival; OP15  
 Hemorrhagic Disease of the Newborn; P71  
 Hemorrhagic Shock; A12, ER3  
 Hemorrhagic Stroke; N43  
 Hemorrhoids; GS38  
 Hemosiderin; H13  
 Hemostasis; H24  
 Hemothorax; ER12  
 Henderson-Hasselbach Equation; CP3  
 Henoch-Schönlein Purpura; NP24, P99  
 Heparin; H33  
 Heparin-Induced Thrombocytopenia; H27  
 Hepatic Encephalopathy; G38  
 Hepatic Failure; G36  
 Hepatic Infarct, Hematoma and Rupture; OB19  
 Hepatitis; G29, NP25  
 Hepatitis, Alcoholic; G34  
 Hepatobiliary Disease; G28  
 Hepatocellular Carcinoma; GS43  
 Hepatoma; GS43  
 Hepatomegaly; G29  
 Hepatopulmonary Syndrome; G37  
 Hepatorenal Syndrome; G37  
 Hepatotoxins; G32  
 Herbal Products; FM52  
 Hereditary Elliptocytosis; H21  
 Hereditary Non-Polyposis Colorectal Cancer; GS34  
 Hereditary Spherocytosis; H21  
 Hernia; GS12, GS22  
   Congenital; GS61  
   Diaphragmatic; P72  
   Hiatus; GS12  
   Inguinal; GS64  
   Umbilical; GS63  
 Herniation Syndrome; NS7  
 Herpes Simplex; D28, P58  
 Herpes Simplex Encephalitis; M121  
 Herpes Simplex Keratitis; OP18  
 Herpes Simplex Virus of Vulva; GY28  
 Herpes Zoster; D29, N37, OP19  
 Herpes Zoster Oticus; OT22  
 Hesselbach's Triangle; GS22  
 Heterophoria; OP39  
 Heterotopic Ossification; OR6  
 Heterotropia; OP38  
 HIDA Scan; M127  
 Highly Active Antiretroviral Treatment; ID44  
 Hill-Sachs Lesion; OR11  
 Hinchey Staging; GS32  
 Hip Arthritis; OR27  
 Hip Dislocation; OR26, OR28  
 Hip Fracture; OR26  
 Hirschberg Test; OP6  
 Hirschsprung's Disease; GS63  
 Histoplasmosis; ID28  
 Histrionic Personality Disorder; PS32

- HIV; ID41, P57  
Prevention; ID45  
HIV-Associated Renal Disease; NP25  
HIV Retinopathy; OP35  
Hives; D41  
Hoarseness; OT8, OT27  
Hodgkin Lymphoma; H43  
Hoffman Reflex; N2  
Hordeolum; OP13  
Hormonal Synthesis; NP2  
Hormone Replacement Therapy; FM42, GY33  
Horner's Syndrome; OP30, OP31, OP32  
Hospitalization, Sequelae of; GM8  
House-Brackmann Grading; OT21  
HPV Infection; D30  
HPV Vaccine; GY44  
H. pylori Ulcer; G13  
Human Immunodeficiency Virus; ID41  
Human Leukocyte Antigen; RH2  
Human Papillomavirus; GY27  
Humeral Fracture; OR15  
Humeral Shaft Fracture; OR16  
Hunt and Hess Grade; NS18  
Huntington's Disease; N27  
Hyaline Membrane Disease; P77  
Hydatidiform Mole; GY48  
Hydatid Liver Cysts; GS42  
Hydrocele; GS61, U28  
Hydrocephalus; MI19, NS8  
Pediatric; NS36  
Hydronephrosis; U6  
Hyperaldosteronism; E32  
Hyperandrogenism; E34, GY12  
Hyperbilirubinemia; P73  
Hypercalcemia; ER36, E39  
Hypercapnea; A11  
Hypercapnia; R25  
Hypercholesterolemia; E3  
Hypercoagulable Disorders; H34  
Hypercoagulable States; C44  
Hypercortisolism; E33  
Hyperemesis Gravidarum; OB18  
Hyperkalemia; C8, ER36, NP12  
Hyperleukocytosis; P53  
Hyperlipidemia; E4, FM8  
Hypermagnesemia; E42  
Hypernatremia; ER36, NP7, NP10  
Hyperopia; OP9  
Hyperosmolar Hyperglycemic State; ER35, E11  
Hyperparathyroidism; E38, MI25  
Hyperphosphatemia; E41  
Hyperplasias, Atypical; GS55  
Hyperprolactinemia; E18  
Hypersensitivity Pneumonitis; R14  
Hypertension; FM37, GM8, NP30  
Pediatric; P85  
Pregnancy; OB15  
Hypertension Encephalopathy; N43  
Hypertension, Intracranial; NS10  
Hypertension, Intraoperative; A13  
Hypertension, Portal; G38  
Hypertension Retinopathy; OP37  
Hypertensive Emergency; ER36  
Hypertensive Nephrosclerosis; NP31  
Hypertensive Urgency; ER37  
Hyperthermia; A11  
Hyperthyroidism; E22  
Hyperthyroidism, Congenital; P29  
Hypertiglyceridemia; E4  
Hypertrophic Cardiomyopathy; C36  
Hypertrophic Pyloric Stenosis; GS61  
Hypertrophic Scar; D8  
Hyperuricemia; RH25  
Hyperviscosity Syndrome; H49  
Hyphema; OP43  
Hypocalcemia; ER36, E40  
Hypocapnea; A11  
Hypochondriasis; PS27  
Hypoglossal Nerve; N11  
Hypoglycemia; ER36, E14  
Neonatal; P72  
Hypogonadism; E18, E47  
Hypokalemia; C8, ER36, NP11  
Hypomagnesemia; E42  
Hyponatremia; ER36, NP7, NP8  
Hypophosphatemia; E41  
Hypoplastic Left Heart Syndrome; P20  
Hypospadias; U38  
Hypotension; A12  
Hypothermia; A11, C8, ER44  
Hypothyroidism; E22, E26  
Hypothyroidism, Congenital; P30  
Hypotonia; P89  
Hypoventilation Syndromes; R31  
Hypoxemia; R6, R25  
Hy's Law; G32  
Hysterectomy; GY11  
Hysterosalpingogram; MI17  
Hysterosalpingography; GY8  
Hysteroscopy; GY10  
Ichthyosis Vulgaris; D23  
Identity Disorder; PS27  
Idiopathic Inflammatory Myopathy; RH15  
Idiopathic Intracranial Hypertension; NS10  
Idiopathic Myelofibrosis; H40  
Idiopathic Pulmonary Fibrosis; R13  
Idiopathic Pulmonary Arterial Hypertension; R17  
Ileal Conduit; GS37  
Ileocecal Valve; MI12  
Ileostomy; GS37  
Ileum; G3  
Imidazoles; ID53  
Immobility; GM9  
Immune Mechanisms of Disease; RH2  
Immune Reconstitution Syndrome; ID40  
Immune Thrombocytopenic Purpura; H26, P49  
Immune Transfusion Reactions; A16  
Immunization; P3  
Geriatric; GM9  
during Pregnancy; OB10  
Immunocompromised Host Infections; ID39  
Immunogenetics; RH2  
Immunologically Mediated Disorders; RH2  
Impaired Driving; GM10  
Impedance Audiometry; OT11  
Impetigo; D25  
Implantable Cardioverter Defibrillators; C21  
Incidentaloma; GS59  
Incontinence; GM7  
Incontinence, Urinary; U6  
Increased Intracranial Pressure; ER5, N39  
Incretin Therapy; E8  
Induction; A9  
Induction Agents; A25  
Infantile Colic; P11  
Infantile Spasms; P86  
Infant Mortality Rate; PH7  
Infarction; C7  
Infections  
Hand; PL23  
Soft Tissue; PL14  
Infectious Diseases  
During Pregnancy; OB20  
Gynecological; GY24  
Management; FM53, ID55  
Nosocomial; ID7  
Outbreak; PH18  
Pediatric; ER59  
Prevention; ID6  
Reportable; PH25  
Transmission; ID6  
Infectious Mononucleosis; P60  
Infectious Pediatric Exanthems; P58  
Infective Endocarditis; C38, ID17, NP25  
Inferior Vena Cava Filter; MI29  
Infertility  
Female; GY22  
Male; E47, GY23, U34  
Inflammatory Bowel Disease; G19, GS29  
Influenza; ID10  
Inguinal Anatomy; GS22  
Inguinal Hernia; U28  
Inhalation Injury; ER46  
Injury Prevention Counselling; P7  
Inner Ear Diseases; OT18  
Innovation-Diffusion Theory; PH6  
Insomnia; FM48, N41  
Instructional Advance Directives; ELOAM8  
Insulin; E8  
Insulinoma; GS60  
Integrated Prenatal Screen; OB6  
Intellectual Disability; P23  
Intensive Care; R32  
Intention-To-Treat; PH9  
Internuclear Ophthalmoplegia; N13  
Interstitial Lung Disease; MI7, R12  
Drug-Induced; R15  
Radiation-Induced; R15  
Interstitial Nephritis; NP28  
Interventional Radiology; MI28  
Interventions; PH10  
Intestinal Atresia; GS63  
Intestinal Ischemia; GS28  
Intra-Abdominal Abscess; GS12  
Intracerebral Hemorrhage; NS20  
Intracoronary Stent; C28  
Intracranial Aneurysms; NS21  
Intracranial Blood; NS16  
Intracranial Hemorrhage; NS18  
Intracranial Hypertension; NS10  
Intracranial Mass Lesions; NS4  
Intracranial Pressure; NS4  
Elevated; NS6  
Treatment; NS7  
Measurement; NS6  
Intraductal Papilloma; GS54  
Intraoperative Bradycardia; A12  
Intraoperative Hypertension; A13  
Intraoperative Hypotension/Shock; A12  
Intraoperative Management; A10  
Intraoperative Tachycardia; A11  
Intraparenchymal Hemorrhage; MI19  
Intrauterine Device; GY21  
Intrauterine Fetal Death; OB42  
Intrauterine Growth Restriction; OB29  
Intravenous Fluids; A14  
Intravenous Induction Agents; A6  
Intraventricular Conduction Abnormalities; C6  
Intraventricular Hemorrhage; P73  
Intubation; A8, ER50  
Intussusception; GS64, P39  
Iodine; MI3  
Iris, Disorders of; OP30  
Iritis; OP5, OP20, OP32  
Iron Deficiency Anemia; G26, H14, OB13, P47  
Iron Indices; H12  
Iron Metabolism; H12  
Irritable Bowel Syndrome; G23, P37  
Ischemia; C7  
Ischemia, Intestinal; GS28

Ischemic Cerebral Infarction; NS18  
 Ischemic Heart Disease; C22, FM19  
 Ischemic Renal Disease; NP17  
 Ischemic Stroke; N43  
 Ischemic Stroke Prevention; N45  
 Ishikawa Diagrams; PH17  
 Isoimmunization Screening; OB7

## J

Janeway Lesions; ID17  
 Janz Syndrome; P87  
 Jaundice; G6, G40, GS6  
   Neonatal; P73  
   Pregnancy; OB19  
 Jehovah's Witnesses; ER6  
 Jejunos; G3  
 Jobe's Test; OR12  
 Jock Itch; D27  
 Joint Anatomy/Pathology; RH2  
 Joint Deformities; RH9  
 Joint Pain; ER25, FM35, OR4, RH3  
 Joint Sepsis; OR10  
 Jones Criteria; P61  
 Justice; ELOAM3  
 Juvenile Idiopathic Arthritis; P98  
 Juvenile Myoclonic Epilepsy; P87

## K

Kaposi's Sarcoma; OP34  
 Karnofsky Performance Scale; NS13  
 Katayama fever; ID36  
 Kawasaki Disease; D41, P58, P100  
 Kayser-Fleischer Ring; G33, OP19  
 Kegel Exercises; GY32  
 Kehr's Sign; GS53  
 Keloid; D8  
 Keratitis; OP5  
 Keratoacanthoma; D7, D35  
 Keratoconjunctivitis Sicca; OP11  
 Keratoconus; OP19  
 Keratosis; D7, D32  
 Kerley Lines; MI7  
 Kernicterus; P75  
 Kernig's Sign; ID19  
 Ketamine; A25, PS25  
 Ketoacidosis; E11, NP15  
 Kidney Function; NP2  
 Kidney Injury; NP33  
 Kidney Stones; ER40  
*Klebsiella pneumoniae*; ID7  
 Kleihauer-Betke Test; OB26  
 Klein's Line; OR39  
 Klinefelter Syndrome; P43  
 Klumpke's Palsy; PL28  
 Knee; OR29  
   Dislocation; OR32  
   Ligament Tears; OR30  
 Koebner phenomenon; D4

## L

Labour; OB31  
   Abnormal Progression; OB43  
   Augmentation; OB37  
   Induction; OB36  
   Lacerations; OB47  
   Pain Management; OB33  
   Preterm; OB38  
 Labyrinthitis; OT12, OT14  
 Laceration; ER18  
 Lachmann Test; OR29  
 Lacrimal Apparatus; OP11  
 Lactase Deficiency; P37  
 Lactic Acidosis; NP15  
 Lactose Intolerance; P37  
 Lambert-Eaton; N32, N33  
 Language Delay; P23  
 Laparoscopy; GY10  
 Large Bowel; G3  
 Large Bowel Obstruction; GS26  
 Large Vessel Kidney Disease; NP17  
 Large Vessel Vasculitis; RH17  
 Laryngeal Mask Airway; A8  
 Laryngeal Papillomas; OT29  
 Laryngitis, Acute; OT27  
 Laryngitis, Chronic; OT28  
 Laryngomalacia; OT46  
 Laryngoscopy; A8  
 Laryngotracheobronchitis; OT44, P92  
 Lead Poisoning; H16  
 Learning Disabilities; P25  
 Leber's Congenital Amaurosis; OP25  
 Le Fort Classification; PL30  
 Left Shift; H4  
 Legg-Calvé-Perthes Disease; OR40  
 Leiomyomata; GY17  
 Lennox-Gastaut; P87  
 Leopold's Maneuvers; OB5  
 Leprosy; ID24  
 Leptomenigitis; MI21  
 Leukemia; P51  
   Acute Lymphoblastic; H41  
   Acute Myeloid; H35  
   Chronic Lymphocytic; H46  
   Chronic Myeloid; H38  
 Leukemoid Reactions; H10  
 Leukocoria; OP41  
 Leukoplakia; D33  
 Level of Consciousness, Altered; ER20  
 Levels of Evidence; PH17  
 Lewy Body Dementia; N20  
 Lhermitte's Sign; N47  
 Lice; D28  
 Licensing Authorities; ELOAM18  
 Lichen Planus; D17  
 Lichen Simplex Chronicus; D17  
 Lid Carcinoma; OP34  
 Lid Swelling; OP12  
 Life Expectancy; PH7  
 Lift-off Test; OR12  
 Ligament of Treitz; G25  
 Light; OP4  
 Light Chain Disease; H48  
 Light's Criteria; R21  
 Likelihood Ratio; PH9  
 Limb Ischemia; C44  
 Limb Pain; NS24, P96  
 Linear Regression; PH15  
 Lipase; G44  
 Lipid Transport; E2  
 Lipid Values; FM9  
 Lipoproteins; E3  
 Lithium Toxicity; PS47

Liver; G3  
   Abscess; GS42  
   Adenoma; GS43  
   Cysts; GS42  
   Disease; H30  
     Drug-Induced; G32  
   Failure; G36  
   Function Test; G28  
   Hemangioma; GS43  
   Mass; MI14  
   Transplantation; GS44  
 Liver Spot; D8  
 Loa Loa; ID35  
 Local Anesthetic Agents; A21, A28  
 Local Infiltration; A22  
 Lofgren's Syndrome; R14  
 Logistic Regression; PH15  
 Loop of Henle; NP3  
 Loss of Consciousness; C4  
 Lou Gehrig's Disease; N30  
 Lower Gastrointestinal Bleeding; P40  
 Lower Limb Ulcers; PL15  
 Lumbar Disc Herniation; OR24  
 Lumbar Disc Syndrome; NS26  
 Lumbar Puncture; N7  
 Lumbar Radiculopathy/Neuropathy; OR22  
 Lumbar Spinal Stenosis; NS27  
 Lund-Browder Chart; PL17  
 Lung Cancer; R27  
 Lung Transplantation; GS16  
 Lung Volumes; R4  
 Lung X-Ray; MI5  
 Lupus Nephritis; NP24  
 Luteinizing Hormone; E18  
 Lyme Arthritis; P99  
 Lyme Disease; ID26  
 Lymphadenopathy; H11, P53  
 Lymphatic Malformation; OT34  
 Lymphedema; C52  
 Lymph Nodes; H11  
 Lymphocytes; H4  
 Lymphocytosis; H9  
 Lymphoid Malignancies; H41  
 Lymphomas; H42, P51  
 Lymphopenia; H9  
 Lymphoplasmacytic Lymphoma; H49  
 Lynch Syndrome; GS34

## M

Macrocytic Anemia; H22  
 Macroglobulinemia; H46  
 Macrolides; ID46  
 Macroscopic (Gross) Hematuria; U4  
 Macrosomia; OB30  
 Macular Degeneration; OP26  
 Macular Edema; OP35  
 Magnetic Resonance Imaging; MI3  
 Major Depressive Disorder; PS10  
   Neurosurgery; NS39  
   Pediatric; PS34  
 Major Depressive Episode; PS9  
 Major Histocompatibility Complexes; RH2  
 Malabsorption; G17  
 Malaria; ID33, ID38  
 Maldigestion; G17  
 Malignant Hyperthermia; A24  
 Malignant Melanoma; D35, PL5  
 Malignant (Necrotizing) Otitis Externa; OT16  
 Malignant Ocular Melanoma; OP34  
 Mallet Finger; PL24  
 Mallory-Weiss Tear; G27, GS14  
 Malnutrition; GM9

Malrotation of Intestine; GS62  
 Mammary Duct Ectasia; GS55  
 Mammography; MI30  
 Mandibular Fractures; PL29  
 Mania; PS10  
 Manic Episode; PS10  
 Mantle Cell Lymphoma; H44  
 Marcus Gunn Pupil; OP33  
 Marijuana Dependence/Abuse; PS25  
 Marjolin's Ulcer; PL9  
 Markowitz-Manson Classification; PL31  
 Mastitis; OB51  
 Mastoiditis; OT17  
 Maternal Mortality Rate; PH7  
 Maternal Serum Screen; OB6  
 Maternal Triage Assessment; OB31  
 Maxillary Fractures; PL30  
 McBurney's Sign; GS28  
 McMurray's Test; OR30  
 MCP Dislocations; PL26  
 MDMA; PS25  
 Measles; D41, P58  
 Mechanical Obstruction in Bowel; MI12  
 Mechanical Ventilation; R26  
 Meckel's Diverticulum; GS62  
 Meconium; OB42  
 Meconium Aspiration Syndrome; P77  
 Mediastinal Mass; MI9, R20  
 Mediastinitis; R21  
 Medicaid/Medicare Program; ELOAM21  
 Medical Certification; ELOAM19  
 Medical Error; ELOAM11  
 Medications during Pregnancy; OB10  
 Medium Vessel Vasculitis; RH17  
 Medullary Sponge Kidney; NP32, U19  
 Melanoma; D9, D35  
 Melasma; D9  
 Melena; G26  
 Menière's Disease; OT12, OT13  
 Meningeal Irritation; N39  
 Meningioma; NS13  
 Meningitis; ER24, ID19, P62  
 Meningocele; NS36  
 Meningococemia; D41, ER43  
 Meniscal Tears; OR31  
 Menopause; FM42, GY32  
 Menstrual Cycle; GY4  
 Mental Status Exam; PS3  
 Mercedes-Benz Sign; OR11  
 Mesenteric Venous Thrombosis; GS28  
 Mesothelioma; R24  
 Meta-Analysis Study; PH13  
 Metabolic Acidosis; ER51, NP15, R5  
 Metabolic Alkalosis; NP16, R5  
 Metabolic Bone Disease; E42, MI24  
   Medications; E54  
 Metabolic Disease; P45  
 Metabolic Syndrome; E15  
 Metastatic Brain Tumours; NS12  
 Metastatic Gastric Carcinoma; GS19  
 Metatarsal Fracture; OR38  
 Methamphetamine; PS26  
 Methicillin-Resistant *Staphylococcus aureus*; ID7  
 Microangiopathic Hemolytic Anemia; H21  
 Microbubbles; MI3  
 Microcytic Anemia; H12  
 Microscopic Hematuria; U5  
 Microscopic Polyangiitis; NP24  
 Middle Ear Diseases; OT17  
 Migraine; FM36  
 Migraine Headache; N39, N40  
 Milia; P78  
 Milk Protein Allergy; P37  
 Mineralization Defect; E45  
 Mineralocorticoid Excess Syndromes; E32

Minimum Alveolar Concentration (MAC); A6  
 Miosis; OP32  
 Mirel's Criteria; OR45  
 Mirizzi Syndrome; GS47  
 Miscarriage; ER40  
 Mitral Regurgitation; C39  
 Mitral Stenosis; C39  
 Mitral Valve Prolapse; C40  
 Mixed Connective Tissue Disease; RH16  
 Mobitz; C14  
 Model for End-Stage Liver Disease; GS44  
 Modified Duke Criteria; ID17  
 Modified Light's Criteria; R21  
 Mole; D9  
 Molluscum Contagiosum; D29  
 Mongolian Spots; P78  
 Monilia; GY25  
 Monitoring Anesthesia; A5  
 Monoarthritis; RH3  
 Monoclonal Gammopathy of Unknown Significance; H49  
 Mononucleosis; ID38, P60  
 Monteggia Fracture; OR18  
 Montgomery Tubercle; GS55  
 Mood Disorders; PS9  
 Mood Stabilizers; PS47  
 Morbidity/Mortality. Causes of; GM2  
 Motor Deficits; N3  
 Motor Exam; N2  
 Motor Neuron Disease; N30  
 Motor Vehicle Collision; ER7  
 Movement Disorders; N24  
   Neurosurgery; NS39  
 Movements, Fetal; OB12  
 Multiaxial Assessment; PS4  
 Multifocal Atrial Tachycardia; C16  
 Multinodular Goitre, Toxic; E25  
 Multiple Endocrine Neoplasm (MEN); E36  
 Multiple Gestation; OB28  
 Multiple Myeloma; H47, NP30, OR44  
 Multiple Sclerosis; MI21, N46  
   Optic Neuritis; OP37  
 Mumps; P63  
 Murmurs; P21  
 Muscle Diseases; N34  
 Muscle Relaxants; A7, A27  
 Muscle Strength/Weakness; N3  
 Muscle Weakness; N7  
 Muscular Dystrophy; P44  
 Musculoskeletal System Imaging; MI22  
 Myasthenia Gravis; N32  
 Mycology; ID5  
 Mycoses, Endemic; ID28  
 Mycosis fungoides; D36  
 Mydriasis; OP32  
 Mydriatic Pupil; OP31  
 Myelodysplastic Syndromes; H36  
 Myelofibrosis; H40  
 Myelography; MI19  
 Myeloma; H46  
 Myelomeningocele; NS36  
 Myeloproliferative Neoplasms; H37  
 Myocardial Disease; C35  
 Myocardial Infarction; C24, ER23, GS11  
   Complications; C27  
 Myocardial Injury; ER12  
 Myocardial Perfusion Scanning; MI27  
 Myocarditis; C35  
 Myoclonus; N25  
 Myopathy; N3, N34  
 Myopia; OP9  
 Myotomes; N6  
 Myotonic Dystrophy; N35  
 Myringotomy; OT39  
 Myxedema Coma; E28

## N

Nail Changes; D39  
 Naloxone; ER50  
 Narcissistic Personality Disorder; PS32  
 Narcolepsy; N42  
 Nasal Discharge; OT23  
 Nasal Obstruction; OT7  
 Nasogastric Tube; MI10  
 Nasolacrimal System Defects; OP41  
 Naso-orbital Ethmoid Fractures; PL31  
 National Institute of Health Stroke Scale; N44  
 Naughton Protocol; C10  
 Nausea; G4, OB18  
 Nausea and Vomiting, Post-Operative; A17  
 Neck Anatomy; OT4  
 Neck Mass; OT8, OT31  
 Neck Masses, Congenital; OT32  
 Neck Triangles; OT4  
 Necrotizing Enterocolitis; P75  
 Necrotizing Fasciitis; ID11, PL14  
 Neer Classification; OR15  
 Neer's Test; OR13  
 Negative Predictive Value; PH9  
 Neglect; ER59  
   Pediatric; P15  
 Nematodes; ID34  
 Neonatal Alloimmune Thrombocytopenia; P70  
 Neonatal Care, Routine; P67  
 Neonatal Resuscitation; P67  
 Neoplasms, see Cancer  
 Neovascular Glaucoma; OP29  
 Nephritic-Nephrotic Spectrum; NP20  
 Nephritic Syndrome; NP22  
   Pediatric; P82  
 Nephroblastoma; P52, U39  
 Nephrolithiasis; ER40  
 Nephron; NP3  
 Nephropathy, Diabetic; E13  
 Nephrosclerosis; NP31  
 Nephrotic Syndrome; NP22  
   Pediatric; P83  
 Nerves; N8  
 Neuralgia; N36  
 Neurapraxia; NS29  
 Neuroanatomy; NS2  
 Neuroblastoma; P52  
 Neurocutaneous Syndromes; P90  
 Neurofibromatosis; D24, P90  
 Neurogenic Bladder; U10  
 Neurogenic Claudication; NS27  
 Neuroleptic Malignant Syndrome; PS43  
 Neurological Exam; N2, NS30  
 Neurologically Determined Death; NS34  
 Neurologic Voiding Dysfunction; U10  
 Neuromuscular Diseases; N3  
 Neuromuscular Junction; A7  
 Neuromuscular Junction Disorders; N32  
 Neuropathic Pain; N36  
 Neuropathy, Diabetic; E13  
 Neuroradiology; MI18  
 Neurotmesis; NS29  
 Neurotrauma; NS30  
 Neutropenia; H8  
 Neutrophilia; H8  
 Neutrophils; H4  
 Nevomelanocytic Nevi; D9  
 Nevus Flammeus; D11  
 Nevus of Childhood; P78  
 Nevus Simplex; D11  
 Newborn, Depressed; P68  
 New York Heart Association (NYHA) Functional Classification of Heart Failure; C31  
 Nicotine Replacement Therapy; FM10  
 Nightmares; P13

Nightstick Fracture; OR19  
 Night Terrors; P13  
 NIH Stroke Scale; N44  
 Nocturnal Myoclonus; PS28  
 Noise-Induced Sensorineural Hearing Loss; OT20  
 Non-Alcoholic Fatty Liver Disease; G35  
 Non-Articular Rheumatism; RH26  
 Non-Hodgkin Lymphoma; H44  
 Non-Maleficence; ELOAM3  
 Non-ST Elevation Myocardial Infarction; C24  
 Non-Stress Test, Fetal; OB12  
 Noonan Syndrome; P43  
 Norepinephrine; CP13  
 Normal Tension Glaucoma; OP28  
 Normocytic Anemia; H16  
 Nose Anatomy; OT3  
 Nose Bleeds; OT26  
 Nosocomial Infections; ID7  
 NSAID; A18  
   Nephropathies; NP28  
   Ulcer; G14  
 Nuclear Cardiology; C10  
 Nuclear Medicine; MI19, MI26  
 Number Needed to Harm/Treat; PH10  
 Numbness; N8  
 Nutrients, Absorption of; G17, G47  
 Nutrition; FM5  
 Nutrition during Pregnancy; OB9  
 Nutrition, Enteral; G47  
 Nutrition, Parenteral; G48  
 Nutrition, Pediatric; P6  
 Nystagmus; N13

## O

Obesity; FM7  
 Obesity, Pediatric; P11  
 Observational Study Designs; PH12  
 Obsessive-Compulsive Disorder; PS16  
 Obsessive Compulsive Disorder Neurosurgery; NS39  
 Obsessive-Compulsive Personality Disorder; PS32  
   Pediatric; PS35  
 Obstetrical Anesthesia; A22  
 Obstructive Sleep Apnea; FM49  
 Occupational Health; PH23  
 Ocular Drug Toxicity; OP44  
 Ocular Emergencies; OP5  
 Ocular Examination; OP5  
 Ocular Imaging; OP9  
 Ocular Metastases; OP34  
 Ocular Pain; OP4  
 Ocular Problems; OP4  
 Ocular Surgery; OP44  
 Ocular Trauma; OP42  
 Oculomotor Nerve; N9  
 Odynophagia; G4  
 Oesophagogastroduodenoscopy; G3  
 Off-Pump Coronary Artery Bypass Surgery; C30  
 Ogilvie's Syndrome; GS27  
 Olecranon Fracture; OR17  
 Olfactory Nerve; N8  
 Oligoarthritis; RH3  
 Oligohydramnios; OB30  
 Oligomenorrhea; GY12  
 Oliguria; GS10  
 Omphalocele; GS62  
*Onchocerca volvulus*; ID34  
 Oncocytoma; U20  
 Onychomycosis; D27, FM45  
 Open Fractures; OR8  
 Open Reduction; OR6  
 Operative Vaginal Delivery; OB46  
 Ophthalmia Neonatorum; OP42

Ophthalmologic Emergency; ER41  
 Ophthalmologic Foreign Body; ER41  
 Ophthalmoscopy; OP8  
 Opioids; A18, A26  
   Antagonists; A19  
 Opioids Dependence/Abuse; PS23  
 Oppositional Defiant Disorder; PS38  
 Optic Disc Atrophy; N12  
 Optic Disc Edema; N11  
 Optic Neuritis; N11  
 Oral Contraceptive Pills; GY19  
 Orbital Cellulitis; ER42, OP10, P65  
 Orbital Floor Fractures; PL31  
 Orchiopexy; U27  
 Orchitis; U15  
 Organ Failure; R32  
 Organs; GS3  
 Orthopedic Emergencies; OR7  
 Orthopedic X-Ray Imaging; OR7  
 Ortolani's Test; OR40  
 Osgood-Schlatter Disease; OR41  
 Osler's Nodes; ID17  
 Osmolar Gap; NP15  
 Osmotic Demyelination; NP8  
 Osteoarthritis; FM43, RH5  
 Osteoblastoma; OR43  
 Osteochondroma; OR43  
 Osteoid Osteoma; OR43  
 Osteomalacia; E45, MI25  
 Osteomyelitis; MI24, OR10  
   Pediatric; P97  
 Osteopenia; MI24  
 Osteoporosis; E42, FM43, MI24  
 Osteosarcoma; OR44  
 Otalgia; ER25, OT6  
 Otitis Externa; OT16  
 Otitis Media with Effusion; OT40  
 Otoacoustic Emissions; OT11  
 Otosclerosis; OT18  
 Ottawa Ankle and Foot Rules; OR38  
 Outbreak of Infectious Diseases; PH18  
 Outerbridge Classification; OR10  
 Ovarian Tumours; GY38  
 Ovaries; GY3  
 Overdose; ER49  
 Overlap Syndrome; RH16  
 Oxygen; ER50  
 Oxygen Therapy; A10  
 Oxytocin; OB37

## P

Pacemaker; C9, C21  
 Packed Red Blood Cells; H51  
 Paget's Disease; E46, MI25  
 Pain; GM13  
   Abdominal; ER19, FM13, G4, G5, GS4  
     Pediatric; ER58, P38  
   Back; FM41  
   Bladder; U13  
   Chest; ER21, FM18  
   Chronic; A19  
   Ear; ER25  
   Joint; ER25, FM35  
   Labour and Delivery; OB33  
   Limb; P96  
   Low Back; FM41  
   Management; A18  
   Neuropathic; A19, N36  
     Neurosurgery; NS40  
   Ocular; OP4  
   Pelvic; ER19, U15  
   Scrotal; U28  
   Pain Disorder; PS27  
   Pain Syndromes; N35  
   Painful Arc Test; OR13  
   Palliative Care; ELOAM13, GM12  
   Palliative Performance Scale; GM12  
   Palpitations; C5  
   Pancoast Tumour; R28  
   Pancreas; G3  
   Pancreatic Cancer; GS51  
   Pancreatic Enzymes; G44  
   Pancreaticoduodenectomy; GS52  
   Pancreatitis; MI15  
     Acute; G44, GS50  
     Autoimmune; G47  
     Chronic; G46, GS51  
   Pancytopenia; H7  
   Panic Attack; PS14  
   Panic Disorder; PS14  
     Pediatric; PS35  
   Papillary Necrosis; NP29  
   Papilledema; N11  
   Pap Test; GY43  
   Papular Acrodermatitis; P58  
   Paradise Criteria; OT43  
   Paralytic Ileus; GS24, GS27  
   Paraneoplastic Syndrome; E51, R28  
   Paranoid Personality Disorder; PS31  
   Paraphasias; N21  
   Paraphilias; PS28  
   Paraphimosis; U30  
   Parapneumonic Effusion, Complicated; R23  
   Parasitic Infections; ID31  
   Parasitology; ID5  
   Parasomnia; FM48, N42  
   Parasympathetic Nervous System; CP13  
   Parathyroidectomy; GS59  
   Parathyroid Hormone; E38  
   Parenteral Nutrition; G48  
   Parietal Lobe Lesions; N22  
   Parkinsonian Disorders; N27  
   Parkinson's Disease; N26  
     Neurosurgery; NS39  
   Parkland Formula; PL19  
   Parotid Gland Neoplasms; OT31  
   Patau Syndrome; P43  
   Patellar Dislocation; OR33  
   Patellar Fracture; OR32  
   Patellofemoral Syndrome; OR33  
   Patent Ductus Arteriosus; P18  
   Patient Controlled Analgesia; A18  
   Patterson-Kelly Syndrome; G10  
   PCP; PS26  
   Pedestrian-Automobile Impact; ER7  
   Pediatric Anesthesia; A23  
   Pediatric Exanthems; D40, P58  
   Pediculosis; D28  
   Pelvic Fracture; OR25  
   Pelvic Inflammatory Disease; GY29  
   Pelvic Mass; GY7  
   Pelvic Pain; ER19, GY7  
   Pelvic Prolapse; GY34  
   Pelvic Relaxation; GY34  
   Pelvis and Perineum Anatomy (Male); U3  
   Pemphigus Vulgaris; D20  
   Penicillins; ID46  
   Penile Tumours; U27  
   Penis Anatomy; U3  
   Peptic Stricture; G9  
   Peptic Ulcer Disease; G12, GS17  
   PERC Score; ER34  
   Percutaneous Biliary Drainage; MI30  
   Percutaneous Biopsy; MI29  
   Percutaneous Coronary Intervention; C25, C28  
   Percutaneous Nephrostomy; MI30  
   Percutaneous Transluminal Angioplasty; MI28



- Perfusion Scan; MI26  
 Pericardial Disease; C42  
 Pericardial Effusion; C42  
 Pericarditis; C8  
 Pericarditis, Acute; C42  
 Pericarditis, Constrictive; C43  
 Perineum; GY2  
 Periodic Health Exam; FM2  
 Periodic Limb Movement Disorder; N42  
 Perioral Dermatitis; D12  
 Periosteal Reaction; MI23  
 Peripheral Arterial Disease; C44  
 Peripheral Facial Paralysis; OT22  
 Peripheral Nerve Blocks; A21  
 Peripheral Nerve Lesions; NS4, NS29  
 Peripheral Nervous System; CP12  
 Peripheral Neuropathy; N3, N31  
 Peripheral Pulmonic Stenosis; P22  
 Peripheral Venous Disease; C50  
 Peritoneal Dialysis; NP36  
 Peritonitis; G40, GS4  
 Peritonsillar Abscess; OT42  
 Pernicious Anemia; H23  
 Persistent Depressive Disorder; PS11  
 Persistent Pulmonary Hypertension of the Newborn; P76  
 Personality Disorders; PS31  
 Pertussis; P64  
 Pervasive Developmental Disorders; PS36  
 Peyronie's Disease; U29  
 Phalanx Fractures; PL25  
 Phalen's Sign; PL27  
 Phalen's Test; N31  
 Pharmacodynamics; CP7  
 Pharmacokinetics; CP3  
     Calculations; CP6  
 Pharmacology, Geriatric; GM13  
 Pharyngitis; FM50, P60  
 Phencyclidine; PS26  
 Phenylketonuria; P46  
 Pheochromocytoma; E36  
 Phimosis; U30  
 Phobia, Pediatric; PS35  
 Phobic Disorders; PS15  
 Photophobia; OP4  
 Physical Abuse, Pediatric; P14  
 Physician-Assisted Suicide; ELOAM13  
 Physiologic Anemia; P47  
 Pigmented Skin Lesion; D8  
 Pilonidal Disease; GS40  
 Pinguecula; OP14  
 Pinworm; ID35  
 PIP and DIP Dislocations; PL26  
 Pituitary Adenoma; E19, NS14  
 Pituitary Hormones; E16  
 Pityriasis Rosea; D17  
 Pityriasis (Tinea) Versicolor; D31  
 Pivot Shift Sign; OR30  
 Placenta; OB2  
 Placental-Site Trophoblastic Tumour; GY49  
 Placenta Previa; OB25, OB26  
 Placenta, Retained; OB49  
 Plain Films Imaging; MI2  
 Plantar Fasciitis; OR37  
 Plasma Anion Gap; NP15  
 Plasma Cholinesterase; A7  
*Plasmodium spp.*; ID33  
 Platelet Products; H51  
 Platelets; H4  
 Platelet Transfusion; H51  
 Plethysmography; R4  
 Pleural Effusion; MI8, R21  
 Plummer-Vinson Syndrome; G10, H14  
 Pneumoconioses; R15  
*Pneumocystis jiroveci*; ID29  
 Pneumonia; GS10, ID8  
     Pediatric; P93  
 Pneumonitis; GS10  
 Pneumothorax; ER11, ER12, MI8, R23  
 Poison Prevention; P12  
 Polyarteritis Nodosa; RH19  
 Polyarthritis; RH3  
 Polycystic Kidney Disease; U19  
 Polycystic Liver Disease; GS42  
 Polycythemia Vera; H39  
 Polyenes; ID53  
 Polyhydramnios; OB30  
 Polymyalgia Rheumatica; RH26  
 Polymyositis; RH15  
 Polypharmacy; GM14  
 Polyps, Colorectal; GS33  
 Ponseti Technique; OR41  
 Populations, Vulnerable; PH3  
 Porphyria Cutanea Tarda; D21  
 Portal Hypertension; G38  
 Port-Wine Stain; D11  
 Positive End Expiratory Pressure; R27  
 Positive Predictive Value; PH9  
 Positron Emission Tomography Scans; MI3  
 Posterior-Cuff Test; OR13  
 Posterior Urethral Valves; U36  
 Posterior Vitreous Detachment; OP22  
 Postherpetic Neuralgia; N37  
 Post-Obstructive Diuresis; U11  
 Postpartum Blues; OB51, PS12  
 Postpartum Care; OB52  
 Postpartum Depression; OB51, PS12  
 Postpartum Hemorrhage; OB48  
 Postpartum Psychosis; OB51  
 Postpartum Pyrexia; OB50  
 Post-Streptococcal Glomerulonephritis; P62  
 Post-Traumatic Stress Disorder; PS17  
     Pediatric; PS35  
 Postvagotomy Diarrhea; GS21  
 Potassium Homeostasis; NP11  
 Potential Years of Life Lost; PH7  
 Power (Probability); PH14  
 Powers of Attorney; ELOAM8  
 Prader-Willi Syndrome; P44  
 Precede-Proceed Model; PH18  
 Precocious Puberty; P32  
 Preconception Counselling; OB4  
 Preeclampsia; OB16  
 Pre-Excitation Syndromes; C18  
 Pregnancy; OB2  
     Bleeding; OB22  
     Emergencies; ER40  
     Diabetes Mellitus; OB13  
     Ectopic; OB23  
     Hypertension; OB15  
     Jaundice; OB19  
     Loss; OB23  
     Prolonged; OB41  
     Termination; OB11  
     Twin; OB28  
 Preen's Sign; U15  
 Premature Atrial/Ventricular Contractions; P21  
 Premature Ejaculation; U32  
 Premature Heart Beats; C16  
 Premature Rupture of Membranes; OB39  
 Premature Ventricular Contraction; C19  
 Premenstrual Dysphoric Disorder; GY5  
 Premenstrual Syndrome; GY5  
 Prenatal Circulation; P16  
 Prenatal Screening; OB5  
 Prenatal Visit; OB4  
 Pre-Operative  
     Assessment; A2  
     Investigations; A3  
     Optimization; A4  
 Pre/Post-Test Probability; PH9  
 Presbycusis; OT19  
 Presbyopia; OP9  
 Preseptal Cellulitis; OP10, P65  
 Pressure Ulcers; GM10, PL16  
 Preterm Labour; OB38  
 Prevalence; PH8  
 Preventive Health Care Grading; PH17  
 Preventive Medicine; PH2  
 Priapism; U29  
 Primary Angle-Closure Glaucoma; OP29  
 Primary Biliary Cirrhosis; G42  
 Primary Hemostasis, Disorders of; H25  
 Primary Open Angle Glaucoma; OP28  
 Primary Pulmonary Hypertension; R17  
 Prinzmetal's Angina; C23  
 Privacy; ELOAM9  
 Prochaska's Stages of Change Model; PH6  
 Prodromal Syndromes; PS6  
 Professional Associations; ELOAM19  
 Progesterone; GY4  
 Progressive Glomerulosclerosis; NP29  
 Prolactin; E18  
 Prolactinoma; GY12  
 Propofol; A25  
 Proportional Mortality Ratio; PH7  
 Proptosis; OP10  
 Prostate Anatomy; U8  
 Prostate Cancer Screening; U25  
 Prostate Specific Antigen; U25  
 Prostatic Carcinoma; U23  
 Prostatitis; U14  
 Prostatodynia; U14  
 Protein C Resistance; H34  
 Protein C/S Deficiency; H34  
 Protein Synthesis Inhibitors; ID49  
 Proteinuria; NP20  
 Prothrombin G20210A; H34  
 Prothrombin Time; G28  
 Protozoa; ID5  
 Protozoa Infections; ID31  
 Proximal Humeral Fracture; OR15  
 Pruritus; D43  
 Pseudocholinesterase, Abnormal; A25  
 Pseudodementia of Depression; PS21  
 Pseudogout; RH24, RH26  
 Pseudohypercalcemia; E38  
 Pseudoseizure; N15  
 Psoriasis; D18  
 Psoriatic Arthritis; RH21, RH23  
 Psychiatric Assessment; PS2  
 Psychiatric Canadian Legal Issues; PS50  
 Psychiatric Emergency; ER55  
 Psychodynamic Therapy; PS40  
 Psychosis; PS6  
     Acute; ER55  
     Postpartum; OB51  
 Psychotherapy; PS39  
 Psychotic Disorder, Brief; PS8  
 Psychotic Disorders; PS6  
 Psychotic Disorder, Shared; PS8  
 Pterygium; OP15  
 Ptoisis; OP13  
 Puberty;  
     Delayed; P33  
     Normal; GY3, P31  
     Precocious; P32  
 Public Health; PH2  
 Puerperal Complications; OB48  
 Puestow Procedure; GS51  
 Pulmonary; R13  
 Pulmonary Contusion; ER12  
 Pulmonary Edema; GS11, MI8  
     Treatment; C32  
 Pulmonary Ejection; P22



Pulmonary Embolism; ER33, GS11, MI8, R17  
 Pulmonary Function Tests; R4  
 Pulmonary Hypertension; R16  
 Pulmonary Nodule; MI7  
 Pulmonary Regurgitation; C40  
 Pulmonary Shunt; R6  
 Pulmonary Stenosis; C40, P19  
 Pulmonary Vasculitis; R20  
 Pulsus Paradoxus; C43  
 Pupil Abnormalities; OP30  
 Pupil, Constricted; OP32  
 Pupil, Dilated; OP32  
 Pupillary Light Reflex; OP30  
 Pupils; OP30  
 Pupils Test; OP6  
 Pure Tone Audiometry; OT9  
 Pus, Cerebral; NS15  
 Pustular Melanosis; P78  
 Pyelonephritis, Acute; U14  
 Pyoderma Gangrenosum; ER43  
 Pyogenic Granuloma; D10  
 Pyrosis; G6

## Q

Q-Angle; OR33  
 Quadriceps/Patellar Tendon Rupture; OR31  
 Quality Adjusted Life Year; PH7  
 Quantitative Research Methods; PH11  
 Quinsy; OT42

## R

Rabies; ID21  
 Raccoon eyes; N2  
 Radial Head Fracture; OR17  
 Radiation during Pregnancy; OB11  
 Radical Prostatectomy; U42  
 Radioactive Iodine Uptake; MI26  
 Radiofrequency Ablation; MI30  
 Radioiodine Ablation; MI26  
 Radionuclide Ventriculography; MI27  
 Radius and Ulna Fracture; OR18  
 Ramsay-Hunt Syndrome; OT22  
 Ramsay Sedation Scale; A6  
 Randomized Controlled Trial; PH13  
 Ranson's Criteria; G45, GS50  
 Rapidly Progressive Glomerulonephritis; NP22  
 Rapid Primary Survey; ER50  
 Rapid Sequence Induction; A9  
 Rash; FM45  
 Rashes, Pediatric; P12  
 Raynaud's Phenomenon; RH12  
 RBC Scan; MI27  
 Reactive Arthritis; P99, RH21, RH23, U16  
 Rectal Prolapse; GS40  
 Rectocele; GY35  
 Red Blood Cells; A15, H3, H51  
 Red Eye; ER41, OP4, OP5  
 Reflexes; N3, P5  
 Reflex Sympathetic Dystrophy; OR6  
 Refraction; OP8  
 Refractive Eye Surgery; OP8  
 Rehydration; P80  
 Reiter's Syndrome; U16  
 Relative Afferent Pupillary Defect; OP33  
 Relative Risk; PH9  
 Relative Risk Reduction; PH10  
 Reliability; PH15  
 Relocation Test; OR11

Renal  
 Adenoma; U20  
 Artery Occlusion; NP17  
 Artery Stenosis; NP17  
 Cell Carcinoma; U20  
 Colic; ER40, U16  
 Diseases, Pediatric; P81  
 Failure; G37, NP35  
 Function; NP2  
 Measurement; NP4  
 Hamartoma; U20  
 Hemodynamics; NP4  
 Parameters; NP3  
 Infarction; NP17  
 Mass; MI16, U19  
 Neoplasms; U19  
 Nuclear Scan; MI17  
 Oncocytoma; U20  
 Osteodystrophy; E46  
 Parenchymal Hypertension; NP31  
 Pelvis Carcinoma; U21  
 Stone; U16  
 Structure; NP2  
 Transplantation; NP37  
 Trauma; U32  
 Tubules; NP3  
 Vein Thrombosis; NP18  
 Renin Release; NP4  
 Reportable Diseases; PH25  
 Reporting Requirements; ELOAM8  
 Research Ethics; ELOAM12  
 Resource Allocation; ELOAM18  
 Respiratory Acidosis; R5  
 Respiratory Alkalosis; R5  
 Respiratory Distress; OT44, R3  
 Neonatal; P76  
 Pediatric; ER57  
 Respiratory Distress Syndrome; P77  
 Respiratory Failure; GS11, R24  
 Respiratory Imaging; MI26  
 Respiratory Tract Diseases; P92  
 Restless Leg Syndrome; N42  
 Restrictive Cardiomyopathy; C37  
 Resuscitation; A13, ER4  
 Retained Placenta; OB49  
 Reticulocytes; H5  
 Retina; OP23  
 Retinal Artery Occlusion; OP23  
 Retinal Detachment; ER42, OP24  
 Retinal Occlusion; ER42  
 Retinal Vein Occlusion; OP24  
 Retinal Zones; OP41  
 Retinitis Pigmentosa; OP25  
 Retinoblastoma; OP41  
 Retinopathy, Diabetic; E12  
 Retinopathy of Prematurity; OP41  
 Retrograde Pyelography; MI17  
 Retrograde Urethrogram; MI17  
 Retroperitoneum; MI11  
 Rett's Disorder; PS37  
 Revascularization, Coronary; C28  
 Reversing Induction Agents; A7  
 Reynold's Pentad; G43, GS48  
 Rheumatic Disease; RH4  
 Rheumatic Fever; C38, P61  
 Rheumatism, Non-Articular; RH26  
 Rheumatoid Arthritis; RH8  
 Rhinitis; OT22  
 Acute; FM19  
 Allergic; FM13, OT23  
 Vasomotor; OT24  
 Rhinorrhea; FM46  
 Rhinosinusitis; OT24  
 Bacterial; OT25  
 Chronic; OT25

Richter's Hernia; GS22  
 Richter's Transformation; H47  
 Rickets; E45, MI25  
 Rigler's triad; GS48  
 Ringworm; D26  
 Rinne Test; OT9  
 Risk Reduction Strategies; PH6  
 Rochester Criteria; P54  
 Rochester Method; OR26  
 Rockwood Classification; OR14  
 Rocky Mountain Spotted Fever; ID27  
 Rohypnol; PS25  
 Rolando's Fracture; PL26  
 Romberg Test; N4  
 Rome III Criteria; G24  
 Roofies; PS25  
 Root Compression; NS24  
 Rosacea; D13, FM45  
 Rosela; P59  
 Rosenthal Syndrome; H29  
 Roseola; D41  
 Rotator Cuff Disease; OR12  
 Rotator Cuff Tests; OR13  
 Roth's Spots; ID17  
 Roundworms; ID34  
 Routine Induction; A9  
 Rouviere's Sulcus; GS46  
 Rubella; D41, P59  
 Rule of 9s; PL17  
 Ruptured Diaphragm; ER12

## S

Sacroiliitis; RH21  
 Sag Sign; OR29  
 Salivary Gland Neoplasms; OT30  
 Salmon Patch; D11, P78  
 Salter-Harris Classification; OR39  
 Sample; PH8  
 SAMPLE; ER5  
 Sarcoidosis; OP38, R13  
 Scabies; D27  
 Scalp Injury; NS31  
 Scaphoid Fracture; OR20  
 Scar; PL9  
 Scarlet Fever; D41, P59, P61  
 Schatzker Classification; OR34  
 Schatzki's ring; G10  
 Schilling Test; H23  
*Schistosoma spp.*; ID35, ID36  
 Schistosomiasis; ID36  
 Schizoaffective Disorder; PS8  
 Schizoid Personality Disorder; PS31  
 Schizophrenia; PS6  
 Pediatric; PS36  
 Schizophreniform Disorder; PS8  
 Schizotypal Personality Disorder; PS31  
 Sciatica; OR24  
 Scintiscan; MI26  
 Scleritis; OP16  
 Scleroderma; G9, NP30, RH8, RH13  
 Sclerosing Cholangitis; G41  
 Scoliosis; OR41  
 Scoliosis Screening; P5  
 Scrotal Mass; U28  
 Scrotum Anatomy; U2  
 SEADS; ER15  
 Seborrheic Dermatitis; FM45  
 Seborrheic Keratosis; D6  
 Secondary Angle-Closure Glaucoma; OP29  
 Secondary Biliary Cirrhosis; G43  
 Secondary Hemostasis, Disorders of; H29  
 Secondary Open Angle Glaucoma; OP29

- Secondary Survey; ER5  
 Sedation; ER60  
 Seddon's Classification; NS29  
 Seizure; ER26, N14  
     Pediatric; P86  
     Febrile; P87  
 Semen Analysis; U36  
 Sensation, Altered; N8  
 Sensitivity; OP4, PH8  
 Sensory Exam; N3  
 Separation Anxiety Disorder; PS35  
 Sepsis; ID22, R33  
     Neonatal; P79  
 Septic Arthritis; ID15, RH5  
     Pediatric; P97  
 Septic Joint; OR10  
 Seroma; GS9  
 Seronegative Rheumatic Disease; RH21  
 Seropositive Rheumatic Disease; RH6  
 Serotonin Syndrome; PS47  
 Sex Chromosome Disorders; P43  
 Sexual Abuse, Pediatric; P15  
 Sexual Assault; ER28  
 Sexual Development; P30  
 Sexual Differentiation Disorders; U39  
 Sexual Dysfunction; GY31  
 Sexually Transmitted Infections; FM46, GY26  
 Sézary Syndrome; D36  
 Shaken Baby Syndrome; OP43  
 Shingles; D29  
 Shock; A12, ER3, R33  
     Neurogenic; NS32  
     Septic; ID22  
     Spinal; NS32  
 Shortness of Breath; ER27, FM29  
 Short Stature; P27  
 Shoulder Dislocation; OR10  
 Shoulder Dystocia; OB44  
 Shoulder Maneuvers; OR12  
 Shunt Complications; NS9  
 Shunt Nephritis; NP24  
 Sialadenitis; OT29  
 Sialolithiasis; OT30  
 Sick Euthyroid Syndrome; E28  
 Sickle Cell Disease; H19, P48  
 Sick Sinus Syndrome; C14  
 Sideroblastic Anemia; H15  
 Silhouette Sign; MI5  
 Silicosis; R15  
 Sinus Arrhythmia/Tachycardia; P21  
 Sinus Block, Pause and Arrest; C14  
 Sinus Bradycardia; C14  
 Sinusitis; FM47, OT24, P65  
 Sinus Tachycardia; C15  
 Sipple's Syndrome; E37  
 Sir Bradford Hill; PH16  
 Sjögren's Syndrome; RH16  
 Skin  
     Anatomy; D2  
     Biopsy; PL7  
     Conditions, Neonatal; P78  
     Eruption; D22  
     Excision; PL7  
     Flaps; PL12  
     Grafts; PL2, PL11  
     Infection; D25  
     Lesions; D3  
         Surgical Management; PL5  
     Reconstruction; PL11  
     Tag; D6  
     Ulcers; PL15  
 Skull Base Osteomyelitis; OT16  
 Skull Bones; PL4  
 Skull Fracture; ER7, NS31  
 Sleep Apnea; FM49, N42, R31  
 Sleep-Disordered Breathing; C34  
     Pediatric; OT41  
 Sleep Disorders; FM48, N41  
 Sleep Disturbances, Pediatric; P12  
 Sleep Requirement; P13  
 Slipped Capital Femoral Epiphysis; OR39  
 Slit-Lamp Examination; OP7  
 Small Bowel Obstruction; GS25  
 Small Vessel Kidney Disease; NP18  
 Small Vessel Vasculitis; RH17  
 Smith's Fracture; OR20  
 Smoke Inhalation; PL19  
 Smoking Cessation; FM10  
 Snellen Acuity; OP5  
 Snoring; FM49  
 Social Anxiety Disorder; PS16  
     Pediatric; PS35  
 Social Phobia; PS16  
     Pediatric; PS35  
 Sodium Homeostasis; NP7  
 Soft Tissue Infections; PL14  
 Soil Contaminants; PH22  
 Solar Keratosis; D7, D32  
 Solar Lentigo; D8  
 Solitary Bone Cyst; OR43  
 Solitary Pulmonary Nodule; R30  
 Somatization Disorder; PS27  
 Somatoform Disorders; PS26  
 Sonohysterography; GY8, MI18  
 Sore Throat; FM50, OT41  
 Specificity; PH8  
 Speech Audiometry; OT10  
 Speech Discrimination Test; OT10  
 Speech Reception Threshold; OT10  
 Spermatocoele; U28  
 Spermatid; GS23  
 Spetzler-Martin AVM Grading Scale; NS23  
 Spherocytosis; H21  
 Spider Angioma; D10  
 Spina Bifida Aperta; NS36  
 Spina Bifida Occulta; NS35  
 Spinal Anesthesia; A20  
 Spinal Cord Injury; NS32  
 Spinal Cord Syndromes; NS28  
 Spinal Dysraphism; NS35  
 Spinal Shock; NS32  
 Spinal Stenosis; OR23  
 Spine Anatomy; NS2  
 Spine Disorders; NS4  
 Spine Fracture; NS33, OR21  
 Splenectomy; GS53  
 Splenic Trauma; GS53  
 Splenomegaly; H12  
 Spondyloarthropathies; RH21  
 Spondylolysis; OR24  
 Spondylolisthesis; OR24  
 Spontaneous Abortion; OB23  
 Spontaneous Bacterial Peritonitis; G40  
 Sprue; G18  
 Spurling's Test; NS25  
 Squamous Cell Carcinoma; D34, GS14, PL5, U22  
 Stab Wound; ER7  
 Stages of Change Model; PH6  
 Standardized Mortality Rate; PH7  
 Staphylococcal Scalded Skin Syndrome; ER42  
 Static Compliance; OT11  
 Statistical Hypotheses; PH14  
 Statistical Significance; PH14  
 Statistical Tests; PH15  
 Status Epilepticus; ER26, N16  
 Steady State; CP6  
 ST Elevation Myocardial Infarction; C24  
 Stenosing Tenosynovitis; PL25  
 Stent; C28  
 Stents; MI28  
 Stevens-Johnson Syndrome; D22, ER43  
 Still's Disease; P98, RH28  
 Still's Murmur; P22  
 Stomach; G2  
 Stomas; GS37  
 Stone Disease; U16  
 Stool Osmotic Gap; G16  
 Strabismus; OP38  
 Stress Echocardiography; C10  
 Stress Fractures; OR39  
 Stress Incontinence; GY36  
 Stress-Induced Ulcer; G14  
 Stress Testing; C10  
 Stridor; OT44  
 Stroke; ER38, MI20, N43  
*Strongyloides stercoralis*; ID35  
 Study Design; PH11  
 Sturge-Weber Syndrome; P91  
 Styte; OP13  
 Subarachnoid Hemorrhage; ER24, MI19, NS18  
 Subconjunctival Hemorrhage; OP15  
 Subdural Hematoma; MI19, NS17  
 Subglottic Stenosis; OT45  
 Substance-Related Disorders; PS21  
 Substitute Decision Makers; ELOAM7  
 Sudden Infant Death Syndrome; P13  
 Suicidal Patient; ER56  
 Suicide; PS4  
 Sulcus Sign; OR11  
 Sulfones; ID51  
 Sunburn; D43  
 Sunscreen; D43  
 Superficial Venous Thrombosis; C50  
 Supraclavicular Arterial Bruit; P22  
 Supracondylar Fracture; OR16  
 Supraventricular Tachyarrhythmias; C15, ER31, P21  
 Surgical Site Infection; GS8  
 Suture; ER17, PL6  
 Swallowing; N10  
 Swan-Ganz Catheter; C11, MI10  
 Swan Neck Deformity; PL24  
 Swimmer's Itch; ID36  
 Sydney Classification of Gastritis; G11  
 Sympathetic Nervous System; CP13  
 Symphysis Fundal Height; OB5  
 Symptom Management; GM12  
 Syncope; ER27, N15  
 Syndrome of Inappropriate Antidiuretic Hormone Secretion; E19, NP9  
 Syndrome X; C23  
 Synovial Fluid Analysis; RH4  
 Syphilis; D31, GY28, ID25, NP25  
 Syringing; OT15  
 Syringomyelia; NS28  
 Syrinx; NS28  
 Systemic Inflammatory Response Syndrome; R33  
 Systemic Lupus Erythematosus; NP24, P99, RH8, RH11  
 Systemic Sclerosis; RH13  
 Systolic Dysfunction; C31  
  
**T**  
 Tachycardia, Intraoperative; A11  
*Taenia saginata*; ID35  
*Taenia solium*; ID35  
 Talar Fracture; OR36  
 Talipes Equinovarus; OR41  
 Tall Stature; P29  
 Tamponade, Cardiac; C43  
 Tanner Stage; GY3, P32  
 T-Cell Lymphoma; H44  
 Tearing, Excessive; OP12

Telogen Effluvium; D37  
 Temperature; A11  
 Temperature, Normal; FM34  
 Temporal Arteritis; ER24, N39, OP38, RH20  
 Temporal Bone Fracture; OT21, OT22  
 Tendons; PL3  
 Tennis Elbow; OR18  
 Tension Pneumothorax; R23  
 Tension-Type Headache; N39  
 Testicular Function; E47  
 Testicular Torsion; U28  
 Testicular Tumours; U26  
 Testosterone Deficiency; E49  
 Tetanus; ID21  
     Prophylaxis; ER17  
 Tetralogy of Fallot; P19  
 Thalassemia; H18  
 Therapeutic Drug Monitoring; CP9  
 Therapeutic Index; CP9  
 Thessaly Test; OR29  
 Thiamine; ER50  
 Thiopental; A25  
 Thoracic Outlet Syndrome; GS15  
 Thoracolumbar Spine; OR22  
 Thoracostomy; GS16  
 Threadworm; ID35  
 Throat Anatomy; OT3  
 Throat, Sore; FM50  
 Thrombocythemia; H40  
 Thrombocytopenia; H6  
 Thrombocytosis; H7  
 Thrombolysis; C25, N44  
 Thrombolytic Therapy; MI29  
 Thromboprophylaxis; R19  
 Thrombosis; C45, C50  
 Thrombotic Microangiopathy; NP19  
 Thrombotic Thrombocytopenic Purpura; H28  
 Thyroglossal Duct Cysts; OT33  
 Thyroid; E20  
     Carcinoma; OT37  
     Gland Anatomy; OT5  
     Imaging/Scans; E22, MI26  
     Medications; E53  
     Nodules; E29  
     Storm; E25  
 Thyroidectomy; GS59  
 Thyroiditis; E24  
 Thyrotoxic Crisis; E25  
 Thyrotoxicosis; E22  
 Thyroxine; E21  
 Tibial Plateau Fracture; OR34  
 Tibial Shaft Fracture; OR34  
 Tic Disorders; N28  
 Tic Douloureux; N36  
 Tick Typhus; ID38  
 Tics; N26  
 Tile Classification; OR25  
 TIMI Risk Score; C24  
 Tinea Capitis; D26  
 Tinea Corporis; D26  
 Tinea Cruris; D27  
 Tinea Manuum; D27  
 Tinea Pedis; D27  
 Tinea Unguium; D27, FM45  
 Tinel's Sign; N31, PL22, PL27  
 Tinnitus; OT7, OT15  
 Tissue Grafts; PL12  
 Tissue Plasminogen Activator (tPA); ER38  
 TLICS Scoring; NS33  
 Tocolysis; OB38  
 Toddler's Diarrhea; P37  
 Toilet Training; P13  
 Tonometry; OP8  
 Tonsillectomy; OT43  
 Tonsillitis; OT41, P60

Topoisomerase Inhibitors; ID50  
 TORCH Infection; OB20  
 Torsades de Pointes; C20  
 Torus Fracture; OR38  
 Total Anomalous Pulmonary Venous Connection; P20  
 Total Body Water; A13  
 Total Hip Arthroplasty; OR28  
 Tourette's Syndrome; N28  
     Neurosurgery; NS39  
 Toxic Epidermal Necrolysis; D22, ER42  
 Toxic Gaps; ER51  
 Toxic Megacolon; GS26  
 Toxicology; ER49  
 Toxic Shock Syndrome; ER42, GY31, ID26  
 Toxidromes; ER52  
*Toxoplasma gondii*; ID34  
 Toxoplasmosis; ID34, OP35  
 Tracheal Intubation; A8  
 Tracheoesophageal Fistula; GS64  
 Tracheostomy; R27  
 Transcranial Magnetic Stimulation; PS50  
 Transfusion; H50  
     Complications; A15  
     Reactions; A16  
     Related Acute Lung Injury; A16  
 Transient Ischemic Attack; OP37  
 Transient Synovitis of the Hip; P97  
 Transient Tachypnea of the Newborn; P77  
 Transitional Cell Carcinoma; U22  
 Transoesophageal Echocardiography; C10  
 Transplant  
     Heart; C34  
     Kidney; NP37  
     Liver; GS44  
     Lung; GS16  
 Transposition of the Great Arteries; P19  
 Transthoracic Echocardiography; C9  
 Transurethral Resection of the Prostate; U42  
 Trauma; NS30, OR7  
     Abdominal; ER13  
     Bladder; U33  
     Brachial Plexus; PL28  
     Chest; ER11  
     Craniofacial; PL28  
     Genitourinary Tract; ER14  
     Hand; PL22  
     Head; ER7, NS30  
     Neck; ER12  
     Ocular; OP42  
     Orthopedic; ER15  
     Pregnancy; ER18  
     Renal; U32  
     Spinal Cord; ER9  
     Spine; ER9  
     Spleen; GS53  
     Temporal Bone; OT21  
     Urethral; U34  
 Traumatic Brain Injury; N22  
 Traveller's Diarrhea; ID14  
 Travel Medicine; ID36  
 Trematodes; ID35  
 Tremor; N25  
     Neurosurgery; NS39  
 Trend; PH14  
 Trendelenburg Sign; OR39  
 Trial of Labour After Cesarean; OB41  
 Triangles of the Neck; OT4  
 Triazoles; ID53  
 Trichiasis; OP13  
*Trichomonas vaginalis*; ID32  
 Trichomoniasis; GY25  
 Trichotillomania; D37  
*Trichuris trichiura*; ID34  
 Tricuspid Regurgitation; C40  
 Tricuspid Stenosis; C40

Trigeminal Nerve; N9  
 Trigeminal Neuralgia; N36  
     Neurosurgery; NS41  
 Triglyceride; FM8  
 Triiodothyronine; E21  
 Trisomy; P43  
 Trochlear Nerve; N9  
 Trousseau's Sign; E40, GS51  
 Truncus Arteriosus; P20  
 Truth Telling; ELOAM11  
*Trypanosoma cruzi*; ID33  
 Tuberculosis; ID23, ID38  
 Tuberos Sclerosis; P91  
 Tube Thoracostomy; GS16  
 Tubular Necrosis; NP28  
 Tubulointerstitial Nephritis; NP25  
 Tumarkin's Otolithic Crisis; OT13  
 Tumour  
     Appendix; GS29  
     Bone; MI23, OR42  
     Brain; NS10  
         Metastatic; NS12  
         Pediatric; NS38  
     CNS; NS10  
     Gastrointestinal; GS19  
     Skin; D33  
     Small Intestine; GS21  
 Tumour Lysis Syndrome; H50  
 Tuning Fork Tests; OT9  
 Turcot Syndrome; GS34  
 Turner Syndrome; P43  
 Twin Pregnancy; OB28  
 Twin-Twin Transfusion Syndrome; OB29  
 Tympanogram; OT11  
 Tympanostomy Tubes; OT39  
 Type I Error; PH14  
 Type II Error; PH14  
 Typhoid Fever; ID38

## U

Uhthoff's Phenomenon; N47  
 Ulcerative Colitis; G19, G22, GS30  
 Ulcers  
     Gastric; GS17  
     Genital; GY28  
     Pressure; GM10  
     Skin; PL15  
 Ulnar Collateral Ligament Injury; PL26  
 Ultrasound; GY8, MI2  
 Ultrasound Pregnancy Screening; OB6  
 Umbilical Cord Prolapse; OB44  
 Urea Concentration; NP5  
 Ureter Carcinoma; U21  
 Ureteropelvic Junction Obstruction; U37  
 Urethral Injuries; U34  
 Urethral Stricture; U9  
 Urethritis; U16  
 Urge Incontinence; GY36  
 Urinalysis; NP5  
 Urinary Abnormalities; NP23  
 Urinary Incontinence; GM8, GY36, U6  
     Pediatric; P9  
 Urinary Retention; GS9, U7  
 Urinary Tract Infection; FM30, U12  
     Pediatric; P65  
     Pregnancy; OB20  
 Urine Electrolytes; NP7  
 Urine Microscopy; NP6  
 Urological Imaging; MI16  
 Urological Procedures; U41  
 Urticaria; D41  
 Usual Interstitial Pneumonia; R13

Uterine Bleeding; GY14  
 Uterine Inversion; OB50  
 Uterine Prolapse; GY35  
 Uterine Rupture; OB45  
 Uterine Sarcoma; GY37  
 Uterus; GY2  
 Uveitis; OP20, OP29

## V

Vaccination; P3  
 Vacuum Aspiration; GY9  
 Vacuum Extraction; OB47  
 Vagal Nerve Stimulation; PS50  
 Vagina; GY2  
 Vaginal Birth After Cesarean; OB41  
 Vaginal Bleed; ER39  
 Vaginal Breech Delivery; OB40  
 Vaginal Cancer; GY47  
 Vaginal Delivery, Operative; OB46  
 Vaginal Discharge; GY6, GY24  
 Vagus Nerve; N10  
 Validity; PH15, PH16  
 Valve Prosthesis; C38  
 Valvular Heart Disease; C38  
 Vancomycin-resistant *Enterococcus*; ID7  
 van Herick Method; OP6  
 Varicella; P59  
 Varices; G37  
 Varices, Esophageal; G26  
 Varicocele; U28  
 Varicose Veins; C50  
 Vasa Previa; OB27  
 Vascular Cerebral Malformations; NS23  
 Vascular Disease; C44  
 Vascular Procedures; MI28  
 Vascular Skin Tumour; D10  
 Vasculitides; P99, RH17  
 Vasoactive Intestinal Peptide-Secreting Tumour; GS60  
 Vasomotor Acute Kidney Injury; NP28  
 Vasomotor Rhinitis; OT24  
 Vaso-Occlusive Crisis; H20  
 Vasospasm; NS20  
 Vault Prolapse; GY35  
 Vegetative State; NS35  
 Venous Hum; P22  
 Venous Sinus Thrombosis; N43  
 Venous Thromboembolism; H31, OB21  
 Venous Thromboembolism, Treatment; H32  
 Venous Ulcers; PL15  
 Ventilation; A10  
 Ventilation, Mechanical; R26  
 Ventilation Scan; MI26  
 Ventricular Assist Devices; C34  
 Ventricular Fibrillation; C20  
 Ventricular Premature Beat; C19  
 Ventricular Septal Defect; P17  
 Ventricular Tachyarrhythmias; C19  
 Ventricular Tachycardia; C19  
 Ventricular Tachydysrhythmias; ER32  
 Vernix Caseosa; P78  
 Verruca; D30  
 Vertigo; FM27, OT5, OT12  
 Vesicoureteral Reflux; U37  
 Vestibular Neuronitis; OT12, OT13  
 Vestibular Schwannoma; NS14, OT14  
 Violence, Domestic; FM28  
 Violent Patient; ER56  
 Virchow's Triad; H31, H32, R17  
 Virology; ID4  
 Visceral Organ Imaging; MI14  
 Vision Loss; OP3, OP4  
 Visual Acuity; OP5

Visual Field, Abnormalities of; N12  
 Visual Fields Tests; OP6  
 Vitamin B12 Deficiency; H22, N18  
 Vitamin D; FM6, FM44  
 Vitamin D Deficiency; E45  
 Vitamin K Deficiency; H30  
 Vitamins, Absorption of; G17  
 Vitamins and Minerals; FM6  
 Vitiligo; D24  
 Vitreous Hemorrhage; OP22  
 Vitritis; OP23  
 Vocal Cord Nodules/Polyps; OT28  
 Vocal Cord Paralysis; OT27  
 Voiding Cystourethrogram; MI17  
 Voiding Dysfunction; U6  
 Voiding Dysfunction, Neurologic; U10  
 Volatile Inhalational Induction Agents; A6, A26  
 Vulvulus; GS36  
 Vomiting; G4  
 Vomiting during Pregnancy; OB18  
 Vomiting, Pediatric; P34  
 von Hippel-Lindau Syndrome; U19  
 von Recklinghausen's Disease; D24  
 Von Willebrand Disease; H28  
 V/Q Scan; MI26  
 Vulnerable Populations; PH3  
 Vulva; GY2  
 Vulvar Cancer; GY46  
 Vulvovaginitis; GY24

## W

WAGR Syndrome; P52  
 Waist Circumference; FM7  
 Waldenström's Macroglobulinemia; H49  
 Waldeyer's Ring; OT40  
 Wallenberg Syndrome; N43  
 Warfarin; H33  
 Warfarin Overdose; ER53  
 Wart; D7, D30  
 Warts, Genital; GY27  
 Waste Excretion; NP2  
 Water Contaminants; PH22  
 Weakness; N7  
 Weakness, Proximal; N34  
 Weber Test; OT9  
 Wegener's Granulomatosis; see Granulomatosis with Polyangiitis  
 Weiss' Ring; OP22  
 Wells Criteria; ER34  
 Wells' Score for VTE; H32  
 Wermer's Syndrome; E37  
 Wernicke-Korsakoff Syndrome; PS23  
 Wernicke's Area; N21  
 Westermark's Sign; R18  
 West Nile Virus; ID27  
 West Syndrome; P87  
 Wet Lung Syndrome; P77  
 Wheezing; FM16  
 Whiplash-Associated Disorders; NS32  
 Whipple Resection; GS52  
 Whipple's Triad; E15  
 Whipworm; ID34  
 White Blood Cells; H4  
 Whitman's Sign; OR39  
 WHO Analgesia Ladder; A18  
 WHO Pain Ladder; N36  
 Wilms' Tumour; P52, U39  
 Wilson's Disease; G33  
 Wolff-Parkinson-White Syndrome; C18  
 Women's Health Initiative; GY34  
 Workplace Health Promotion and Protection; PH23  
 Workplace Legislation; PH24

Wound; PL8  
 Abnormal Healing; PL9  
 Closure; PL9  
 Contaminated/Infected; PL9  
 Dressings; PL11  
 Management; ER17  
 Wound Care; GS7  
 Wound Dehiscence; GS9  
 Wound Hemorrhage/Hematoma; GS9  
 Wright Stain; OB27  
 Wrist Anatomy; PL3  
 Wrist Fracture; OR19  
 Wuchereria bancrofti; ID35

## X

Xanthelasma; OP14  
 X-Ray Imaging; MI2, MI4  
 Abdominal; MI10  
 Bone; MI22  
 X-Ray Imaging, Orthopedic; OR7

## Y

Yeast Infections; D31

## Z

Zenker's Diverticulum; G9  
 Z-Score; MI24  
 Z-Test; PH15  
 Zygomatic Fractures; PL31